PATENT
Docket No. 30060-20042.00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|
| In the application of:<br>Hun Yeong Koh et al.<br>Serial No.: 10/694,843<br>Filing Date: October 29, 2003<br>For: A METHYLIDENE OXAZOLIDINONE COMPOUND AND PREPARATION METHOD THEREOF | Examiner: Taofiq A Solola<br>Group Art Unit: 1626 |

**DECLARATION UNDER 37 CFR 1.131**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Hun Yeong KOH, Yong Seo CHO, Ae Nim PAE, Joo Hwan CHA, Hye Yeon KIM, Jae Seok LEE, Hak Soo KIM and Sanghee KIM, citizens of Korea, declare under penalty of perjury under the laws of the United States of America as follows:

1. We are the inventors on this application.

2. We are familiar with the subject matter and claims of the present application.

3. We have reviewed the Action of December 16, 2004, in which the Examiner rejected claims 1 to 13 as being anticipated by Patel et al., US Provisional application No. 60/395,164.

4. We file this Declaration to antedate Patel.

5. Foremost, please notice that the filing dates of Patel is July 11, 2002. This application claims benefit from Korean Application 66268/2002 filed October 29, 2002.

6. Korean Application 66268/2002 is based on the Report of Invention (invention disclosure) submitted by us on February 26, 2002, to the Korea Institute of Science of Technology (KIST) Patent Management Team. Enclosed herewith are the Korean language copies and the certified English language translations of the Report of Invention, Deed of Assignment and a draft of the patent specification prepared by us that we submitted to the KIST Patent Management Team on February 26, 2002.

7. The invention of this application was reduced to practice before February 26, 2002. Subsequently, we prepared the Report of Invention, Deed of Assignment and a draft of the patent specification and submitted them to the KIST Patent Management Team on February 26, 2002.

8. Based on the data in the draft of the patent specification that we submitted to the KIST Patent Management Team on February 26, 2002, we recognized before February 26, 2002, that the claimed invention would work for the intended purpose of providing a new methylidene oxazolidinone compound having anti-microbial activity and preparation method thereof.

9. The invention of this application was reduced to practice in Korea, a WTO member country, now and at the time of this invention.

We declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed at Seoul, this 7 day of April, 2005.

4/7/05 — Hun Yeong KOH

4/7/05 — Yong Seo CHO

4/7/05 — Ae Nim PAE

4/7/05 — Joo Hwan CHA

4/7/05 — Hye Yeon KIM

4/7/05 _____ _____

Date Jae Seok LEE

4/7/05 _____ _____

Date Hak Soo KIM

4/7/05 _____ _____

Date Sanghee KIM

(Translation)

# REPORT OF INVENTION

| | | | | |
|---|---|---|---|---|
| Tile of the Invention | New Oxazolidinone Derivatives Having Methylidene Pyeridinyl Moiety and the Preparation Thereof | | | |
| Inventor(s) | Belongs to | Position | | Name (and Signature) |
| | KIST | Responsible Researcher | | KOH, Hung Yeong [Sign] |
| | KIST | Responsible Researcher | | CHO, Yong Seo [Sign] |
| | KIST | Senior Researcher | | PAE, Ae Nim [Sign] |
| | KIST | Researcher | | CHA, Joo Hwan [Sign] |
| | KIST | Student Researcher | | KIM, Hye Yeon [Sign] |
| | KIST | Student Researcher | | LEE, Hae Seok [Sign] |
| | KIST | Student Researcher | | KIM, Hak Soo [Sign] |
| | KIST | Student Researcher | | KIM, Sanghee [Sign] |
| Cost of Application | Country to be desired to apply | Amount | Account No. | Responsible Person |
| | KR and US | 4,000,000 | 2N23250 | KIM, Jung Hyup [Sign] |
| Research Subject | Development of Substances to Inhibit Growth of Resistant Bacteria | | Research Period | 8/15/2001-5/14/2002 |
| | | | Account No. | 2N23250 |
| Publication of the Invention | Publication Media | Title of the Publication | Expected Date of Publication | |
| | - | - | - | |
| Agent(s) | Park, Kim & Partner | | | |
| Other | | | | |

We hereby report our invention. Please succeed to this invention.

Attachments: 1. Specification of the Inventions
2. Deed of Assignment
3. Opinion for Utilizing the Invention

This 26th day of February, 2002

| |
|---|
| Manager |
| [Sign] |
| Head of Center |
| [Sign] |
| |
| |

**To: Representative of the Korea Institute of Science and Technology**

# DEED OF ASSIGNMENT

| | | | | |
|---|---|---|---|---|
| Assignee | Address | 39-1, Hawolgok-Dong, Sungbook-Gu, Seoul, Korea | | |
| | Name | Korea Institute of Science and Technology | Resident Registration No. | 114422-0000174 |
| We hereby assign the right to receive a patent in connection with the following invention to the above assignee. | | | | |
| Patent No. | | | | |
| Title of the Invention | | New Oxazolidinone Derivatives Having Methylidene Pyperidinyl Moiety and the Preparation Thereof | | |
| | | This 26th day of February, 2002 | | |
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| | Name | Kim, Hak Soo | Resident Registration No. | 740606-1531117 |
| | Address | Useong Apt. 15-707, Seocho-Dong, Seocho-Gu, Seoul, Korea | | |
| | Name | Kim, Sanghee | Resident Registration No. | 741128-1531117 |

IN THE MATTER OF
US PATENT APPLICATION NO. 10/694,843

I, THE UNDERSIGNED, HEREBY DECLARE:
THAT I AM CONVERSANT WITH BOTH THE KOREAN AND THE ENGLISH LANGUAGES: AND

THAT I AM THE TRANSLATOR OF THE ATTACHED ENGLISH SPECIFICATION AND THAT SAID ENGLISH SPECIFICATION IS A TRUE AND ACCURATE TRANSLATION OF THE INVENTION DISCLOSURE ATTACHED TO THE REPORT OF THE INVENTION SUBMITTED BY THE INVENTORS ON FEBRUARY 26, 2002 TO THE KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY PATENT MANAGEMENT TEAM IDENTIFIED BELOW:

INVENTOR(S): HUN YEONG KOH; YONG SEO CHO; AE NIM PAE;
JOO HWAN CHA; HYE YEON KIM; JAE SEOK LEE;
HAK SOO KIM and SANGHEE KIM

FOR: A METHYLIDENE OXAZOLIDINONE COMPOUND AND PREPARATION METHOD THEREOF

IN WITNESS WHERETO, I SET MY HAND HERETO

THIS 4TH DAY OF APRIL, 2005

BY Seongsu Lee
SEONG-SU LEE

(Translation)

[Attachment 2]

## SPECIFICATION

1. Title of the Invention

New Oxazolidinone Derivatives Having Methylidene Piperidinyl Moiety and Preparation Method Thereof

2. Description of the Drawings

Figure 1 shows structures of the representative compounds of the present invention. Figures 2 and 3 shows a process for synthesizing Compound (I) of the Invention.

3. Detailed Description of the Invention

3.1 Field of the Invention

Presently used antibiotics have been rapidly losing their activities due to the generation of resistant strains. It is because that high-grade antibiotics have been used in order to treat various infectious diseases in hospitals as people have been easily infected by bacteria, and therefore, such misuses of the antibiotics have made various resistant strains increased rapidly. Strains such as methicillin-resistant staphylococcus aureus (MRSA), methicillin-resistant *Staphylococcus epidermis* (MRSE), *Enterococcus pneuminiae*, quinolone-resistant *Staphylococcus aureus* (QRSA), vancomycin-resistant *Enterococcus* (VRE), multi-drug resistant

mycobacterium tuberculosis and the like exhibit resistance globally against the most antibiotics which are presently used. Therefore, there is desperate need for a new antibiotic having a new structure and mechanism which are able to solve the above resistance problem.

Therefore, the present invention relates to a methylidene piperidinyl or pyrrolidinyl oxazolidinone compound or a salt thereof, having anti-microbial activity against gram-positive germs including resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE) and the like, and to a preparation method thereof.

3.2 Background Art and its Problems

In 1987, Dupont Co. reported first that Dup-721, a compound of oxazolidinone derivative, showed activities against MRSA and β-lactamase, and compounds included in such group showed anti-microbial activities. However, development for the Dup-721 as an antibiotic was stopped during clinical trial phase 1 due to its toxicity.

Since then, researches into structures and activities of the oxazolidinone compound has been performed by Pharmacia Upjohn, Merck, Bayer and the like. Linezolid ("LZD"), which is a new antibiotic having a new frame, was developed by Upjohn in April, 2000, and has been sold under brand name "Zybox", which is a new type of antibiotic appeared first since last 35 years. Although the compound shows high pharmaco-kinetic profile, it does not good activity against the resistant strains such as MRSA or VRE.

Therefore, it is required to develop a new compound exhibiting higher activities against wide range of strains which show resistance to conventional

antibiotics.

3.3. Technical Subject of the Invention to Achieve (Object of the Invention)

Therefore, an object of the present invention is to provide a novel methylidene piperidinyl or pyrrolidinyl oxazolidinone compound or a salt thereof, which can be used as an antibiotic exhibiting higher activities against multi-drug resistant strains, and a preparation method thereof.

Another object of the present invention is to provide a novel oxazolidinone compound or a salt thereof, which has higher anti-microbial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Enterococcus pneuminiae*, quinolone-resistant *Staphylococcus aureus* (QRSA), vancomycin-resistant *Enterococcus faecium* (VRE) and the like, and a preparation method thereof.

3.4 Constitution and Action of the Invention

The present invention relates to a novel oxazolidinone compound or a salt thereof, which has higher anti-microbial activities against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), *Enterococcus pneuminiae*, quinolone-resistant *Staphylococcus aureus* (QRSA), vancomycin-resistant *Enterococcus faecium* (VRE) and the like, and a preparation method thereof.

3.5 Effect of the Invention

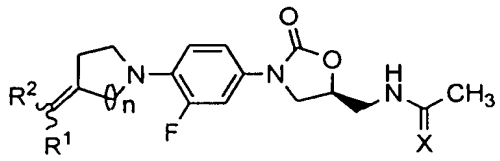
The present invention demonstrated that the compound of the invention shows higher anti-microbial activities against the strains resistant to the prior art

antibiotics. This is an outstanding achievement of the present invention because the compound of the invention can be used to treat strains that cannot be treated with prior art antibiotics.

The compounds of the present invention have simple structures compared with the antibiotics currently used in clinic, and inhibit initial stage of the synthesis of proteins by bacterial strains.

4. Claims

1. A methylidene oxazolidinone compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



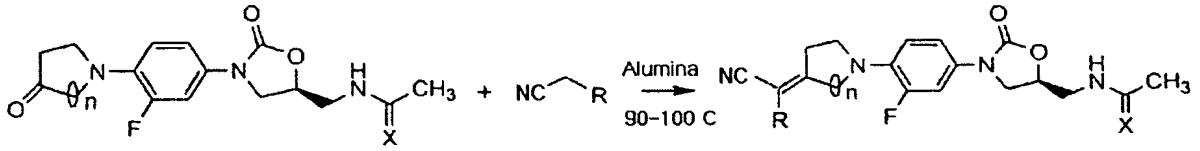
n=1, 2

(I)

wherein X represents an oxygen or sulfur atom; and

$R^1$ and $R^2$ independently represent hydrogen atom, cyano group, alkyl group, halogen atom, acetoxy group, ethoxycarbonyl group, hydroxy group, hydroxyimino group, methoxyimino group or aminoethyl group, or a unsaturated 5-membered heterocyclic substituent containing one or more hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur.

2. A method for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (III):

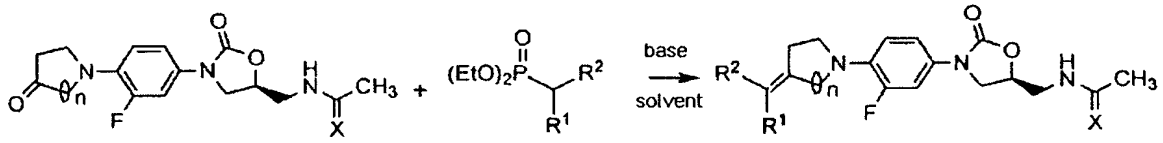



n = 1,2 X = O or S n = 1,2 X = O or S

(II) (III) (I)

wherein the compound of formula (III) is preferably malonitrile, ethylcyano or acetate group. Knoevenagel Condensation to be used in this method is carried out without or with a solvent selected from methylene chloride and benzene, aluminum oxide, amine or the like can be used as a catalyst, and reaction temperature is preferable in the range of 90-100°C. In the above formula, each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

3. A method for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (IV):



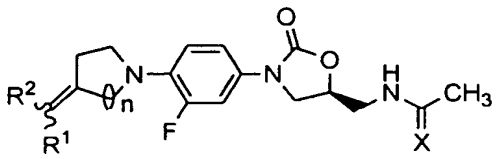

n = 1,2 X = O or S n = 1,2 X = O or S

(II) (IV) (I)

wherein various derivatives represented by formula (IV) can be used. Firstly, it is necessary to activate the compound (IV). That is, by using tetrahydrofuran, dimethylethane, dimethyl formanide or the like as a solvent, and using sodium hydride, potassium t-butoxide or the like as a base, phophonate is activated, and then Wadwards-Horner-Emmons reaction is carried out after adding the compound (II). It is possible to react in the temperature range of 40-100°C, but

preferable temperature is 25°C. In the above formula, each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

4. The compound of claim 1, represented by the following formula (I):



n=1, 2

(I)

wherein each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

5. The compound of claim 4, wherein n is 1.

6. The compound of claim 5, wherein n is 1, including N-[[(5S)-3-[3-fluoro-4-(3-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((3-(1-ethoxycarbonyl-1-cyano)methylidene)pyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,N-[[(5S)-3-[3-fluoro-4-(3-cyano-methylidenepyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((3-(1-methyl-1-cyano)methylidene)pyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, or a hydro-chloride salt thereof.

7. The compound of claim 4, wherein n is 2.

8. The compound of claim 7, wherein n is 2, including N-[[(5S)-3-[3-fluoro-4-(4-(1-cyano-2-ethoxy-carbonylethylidene)piperidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]-

methyl]acetamide, N-[(5S)-3-[3-fluoro-4-(4-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazol-idinyl]methylacetamide, N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-cyano)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-cyanomethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(3-thiophen-2-yl-5-isoxazolyl)methylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(3-(3-methyl-isothiazol-4-yl)-iso-xazolyl)methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-ethoxycarbonyl-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-methylcarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(1-ethoxycarbonylethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, N-[[(5S)-3-[3-fluoro-4-(4-carboxymethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-chloro)methylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(1-cyanoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]- methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminopropyl-idene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyimino-propyl-idene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-

acetoxypropylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-(chloroacetoxy)propylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-(dichloroacetoxy)-propylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(cyano-methylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]thioacetamide, or a hydro-chloride salt thereof.

9. The compound according to claim 1, wherein the pharmaceutically acceptable salt is a methanesulfonate, fumarate, hydrobromide salt, citrate, maleate, phosphate, sulfate, hydrochloride salt or a sodium salt.

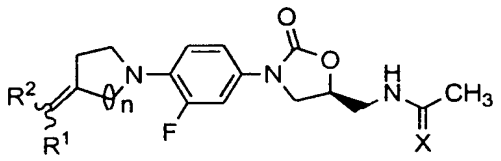
**[Specification]**

[Title of the Invention]

New Oxazolidinone Derivatives Having Methylidene PIperidinyl Moiety and Preparation Method Thereof

[Detailed Description of the Invention]

The present invention relates to a methylidene piperidinyl or pyrrolidinyl oxazolidinone compound represented by the following formula (I) or a salt thereof, and a preparation method thereof:



(I)

wherein X represents an oxygen or sulfur atom;

n represents an integer 1 or 2;

$R^1$ and $R^2$ independently represent hydrogen atom, cyano group, alkyl group, halogen atom, acetoxy group, ethoxycarbonyl group, hydroxy group, hydroxyimino group, methoxyimino group, aminoethyl group or a heterocyclic substituent. In the compound of the above formula (I), the alkyl group may be methyl, ethyl, propyl group or the like, the halogen atom may be chlorine or bromine atom, and the acetoxy group may be substituted with one or more chlorine atoms. In addition, the heterocyclic substituent is a unsaturated 5-

membered heterocyclic group containing one or more hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur, and examples of the heterocyclic substituent may include isoxazole, thiophene, thiazole, isothiazole, thiadiazole and the like.

The present invention also includes a pharmaceutically acceptable salt of the compound of formula (I), and the salt may include a salt of methanesulfonate, fumarate, hydrobromide, citrate, maleate, phosphate, sulfate, hydrochloride or sodium.

Presently used antibiotics have been rapidly losing their activities due to the generation of resistant strains. It is because that high-grade antibiotics have been used in order to treat various infectious diseases in hospitals as people have been easily infected by bacteria, and therefore, such misuses of the antibiotics have made various resistant strains increased rapidly. Strains such as methicillin-resistant staphylococcus aureus (MRSA), methicillin-resistant *Staphylococcus epidermis* (MRSE), *Enterococcus pneuminiae*, quinolone-resistant *Staphylococcus aureus* (QRSA), vancomycin-resistant *Enterococcus* (VRE), multi-drug resistant mycobacterium tuberculosis and the like exhibit resistance globally against the most antibiotics which are presently used. Therefore, there is desperate need for a new antibiotic having a new structure and mechanism which are able to solve the above resistance problem.

In 1987, Dupont Co. reported first that Dup-721, a compound of oxazolidinone derivative, showed activities against MRSA and β-lactamase, and compounds included in such group showed anti-microbial activities. However, development for the Dup-721 as an antibiotic was stopped during clinical trial phase 1 due to its toxicity.

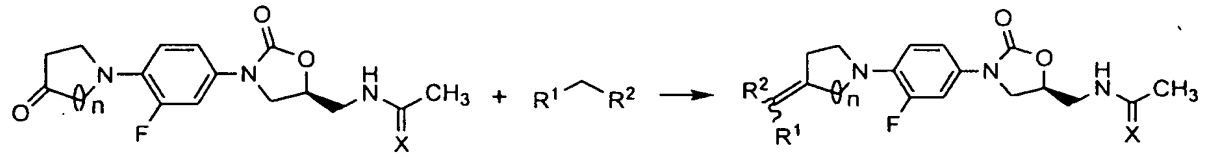
Since then, researches into structures and activities of the oxazolidinone compound has been performed by Pharmacia Upjohn, Merck, Bayer and the like. Linezolid ("LZD"), which is a new antibiotic having a new frame, was developed by Upjohn in April, 2000, and has been sold under brand name "Zybox", which is a new type of antibiotic appeared first since last 35 years. Although the compound shows high pharmaco-kinetic profile, it does not good activity against the resistant strains such as MRSA or VRE.

It was discovered that the compound of the above formula (I) or a salt thereof according to the present invention shows superior activity as twice as the LZD of Upjohn Co. against the MRSA and other Gram-positive germs.

The compound of formula (I) can be prepared by reacting an oxazolidinone intermediate (disclosed in WO 95/25106) represented by the following formula (II) with a compound represented by the following formula (III) or (IV), so as to introduce a methylidene piperidinyl or pyrrolydinyl group thereto.

Methylidene peperidine derivatice can be introduced by the following two methods. In method A, Knoevenagel Condensation was used, and in method B, Wadwards-Hornor-Emmons reaction was used.

Method A: Knoevenagel Condensation

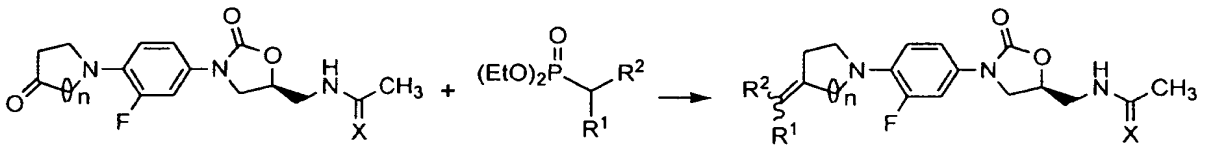


n=1, 2 X = O or S n=1, 2 X = O or S

In the above reaction formula, R is cyano group or ethoxycarbonyl. X is oxygen or sulfur atom. Preferable solvent is methylene chloride or benzene, but

this reaction can be carried out without a solvent. Ammonia, an ammonium salt, amine, piperidine, potassium fluoride, serium fluoride, titanium chloride, aluminum oxide or the like can be used as a catalyst, and reaction temperature is preferable in the range of 50-100°C.

Method B: Wadwards-Horner-Emmons method



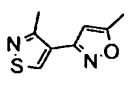
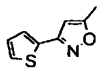
n = 1,2 X = O or S n = 1,2 X = O or S

(II) (IV) (I)

In this method, various derivatives can be introduced. In this method, a process for activating phosphonate is required. In the process for activating the phosphonate, sodium hydride or n-butyllithium can be used as a base, cleanly purified tetrahydrofuran, dimethylethane or the like is preferably used as a solvent, and the temperature is preferably maintained at 0°C or room temperature. After activating the phosphonate, the piperidinone is added thereto, and the resulting mixture is stirred. The reaction can be carried out at room temperature or by refluxing. These all procedures are preferably performed under a nitrogen atmosphere.

Table 1: Synthesized Oxazolidinone Compounds

| Compd. Nos. | $R^1$ | $R^2$ | Compd. Nos. | $R^1$ | $R^2$ | Compd. Nos. | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1[a] | CN | CN | 10 | H |  | 19 | H | $CH(NOCH_3)$ |
| 2[a] | CN | $CO_2Et$ | 11 | H | $CO_2Et$ | 20 | H | $C(NOH)CH_3$ |
| 3[a] | H | CN | 12 | H | $COCH_3$ | 21 | H | $C(NOCH_3)CH_3$ |
| 4[a] | $CH_3$ | CN | 13 | $CH_3$ | $CO_2Et$ | 22 | H | $CH(OH)CH_3$ |
| 5 | CN | $(CH_2CO_2Et)$ [b] | 14 | H | $CO_2Na$ | 23 | H | $CH(OAc)CH_3$ |
| 6 | CN | CN | 15 | Cl | $CO_2Et$ | 24 | H | $CH(OCOCH_2Cl)CH_3$ |
| 7 | CN | $CO_2Et$ | 16 | CN | $CH_3$ | 25 | H | $CH(OCOCHCl_2)CH_3$ |
| 8 | H | CN | 17 | H | CHO | 26 [b] | H | CN |
| 9 | H |  | 18 | H | CH(NOH) | | | |

[a]: n=1, [b]: X = S

Nomenclatures of the compounds 1 - 26 shown in the above table 1, which are representative compounds of the present invention, are as follows:

Compound 1: N-[[(5S)-3-[3-fluoro-4-(3-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Compound 2: N-[[(5S)-3-[3-fluoro-4-((3-(1-ethoxycarbonyl-1-cyano)-methylidene)pyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Compound 3: N-[[(5S)-3-[3-fluoro-4-(3-cyanomethylidenepyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Compound 4: N-[[(5S)-3-[3-fluoro-4-((3-(1-methyl-1-cyano)methylidene)-pyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Compound 5: N-[[(5S)-3-[3-fluoro-4-(4-(1-cyano-2-ethoxycarbonyl-ethylidene)piperidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Compound 6: N-[(5S)-3-[3-fluoro-4-(4-dicyanomethylidenepyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

Compound 7: N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-cyano)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 8: N-[[(5S)-3-[3-fluoro-4-(4-cyanomethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 9: N-[[(5S)-3-[3-fluoro-4-((4-(3-thiophen-2-yl-5-isoxazolyl)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 10: N-[[(5S)-3-[3-fluoro-4-((4-(3-(3-methyl-isothiazol-4-yl)-isoxazolyl)methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 11: N-[[(5S)-3-[3-fluoro-4-(4-ethoxycarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 12: N-[[(5S)-3-[3-fluoro-4-(4-methylcarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 13: N-[[(5S)-3-[3-fluoro-4-(4-(1-ethoxycarbonylethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 14: N-[[(5S)-3-[3-fluoro-4-(4-carboxymethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 15: N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-chloro)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 16: N-[[(5S)-3-[3-fluoro-4-(4-(1-cyanoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 17: N-[[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 18: N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminoethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 19: N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminoethylidene)-

piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 20: N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminopropylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 21: N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminopropylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 22: N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxypropylidene)-piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 23: N-[[(5S)-3-[3-fluoro-4-(4-(2-acetoxypropylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 24: N-[[(5S)-3-[3-fluoro-4-(4-(2-(chloroacetoxy)propylidene)-piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 25: N-[[(5S)-3-[3-fluoro-4-(4-(2-(dichloroacetoxy)propylidene)-piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

Compound 26: N-[[(5S)-3-[3-fluoro-4-(4-(cyanomethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide.

The compound of formula (I) according to the present invention also includes salts of the above compounds 1 - 26.

## EXAMPLES

Example 1) Preparation of N-[[(5S)-3-[3-fluoro-4-(3-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-{3-[3-fluoro-4-(3-oxo-pyrrolidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}acetamide (50 mg, 0.15 mmol), $Al_2O_3$ (200 mg, Basic, I™, Aldrich),

malononitrile (5 g, excess) were mixed, and the resulting mixture was then stirred for 30 minutes at 40°C. The reaction mixture was washed with water and extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate and then concentrated. The concentrated residue was purified by column chromatography (silica, EtOAc:MeOH=40:1), to obtain 29.4 mg of desired product (51% yield).

$^1$H NMR ($CDCl_3$): δ 7.48(d, *J*=14.7, 1H), 7.11(d, *J*=10.5, 1H), 6.78(t, *J*=3.0, 1H), 5.97(s, 1H), 4.78(m, 1H), 4.43(s, 2H), 4.03(t, *J*=9, 1H), 3.74(m, 3H), 3.61(m, 2H), 3.20(t, 2H), 2.00(s, 3H).

Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

Example 2) Preparation of N-[[(5S)-3-[3-fluoro-4-(3-(1-cyano-1-ethoxycarbonyl) methyl-idenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydro-chloride salt thereof

N-{3-[3-fluoro-4-(3-oxo-pyrrolidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}acetamide (50 mg, 0.15 mmol), ethyl cyanoacetate (5 ml, excess) and $Al_2O_3$ (200 mg, Basic, I™, Aldrich) were mixed, and the resulting solution was stirred for 13 hours at room temperature. The reaction mixture was washed with water and then extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate and concentrated. The concentrated residue was purified by column chromatography (silica, EtOAc:MeOH=40:1), to obtain 32.3 mg of desired product (50% yield). Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz): δ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(m, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03 (s, 3H), 1.37(t, J=7.14, 3H).

Example 3) Preparation of N-[[(5S)-3-[3-fluoro-4-(3-cyanomethylidenepyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

Potassium t-butoxide (33.46 mg, 0.30 mmol) was dissolved in 3 ml of THF in a reactor under a nitrogen atmosphere, and the resulting solution was cooled down to –78°C. While the temperature of the reactor was maintained at -78°C, a solution of diethyl cyanomethyl phosphonate (52.83 mg, 0.33 mmol) in 3 ml of THF was slowly added thereto, and the resulting solution was stirred for one hour. A solution of N-{3-[3-fluoro-4-(3-oxo-pyrrolidin-1-yl)phenyl]-2-oxo-oxazolidin-5-ylmethyl}acetamide (500 mg, 1.49 mmol) in 9 ml of THF was added to the reactor for 20 minutes, and the resulting solution was stirred for 3 hours. The reaction was ended by adding water, and the reaction mixture was extracted with ethyl acetate. Organic extract was dried with magnesium sulfate and concentrated under a reduced pressure. The concentrated residue was purified by column chromatography (EtOAc:MeOH=10:1) using silica gel (230 – 400 mesh) neutralized with triethylamine, to obtain 50 mg of desired product (59% yield). Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz): δ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H),

6.80(m, 1H), 6.00(s, 1H), 4.77(m, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03 (s, 3H), 1.37(t, J=7.14, 3H).

Example 4) Preparation of N-(3-{4-[3-(cyano-methyl-methylene)-pyrrolidin-1-yl]-3-fluorophenyl}-2-oxo-oxazolidin-5-ylmethyl)acetamide and hydrochloride salt thereof

Under a nitrogen atmosphere, potassium t-butoxide (133.8 mg, 0.24 mmol) was dissolved in 5 ml of THF, and a solution of diethyl cyanoethyl phosphonate (214.4 mg, 1.22 mmol) in 5 ml of THF was slowly added thereto. The resulting solution was stirred for 30 minutes and then cooled down to –78°C. A solution of N-{3-[3-fluoro-4-(3-oxo-pyrrolidin-1-yl)phenyl]-2-oxo-oxazolidin-5-yl-methyl}acetamide (80.0 mg, 0.24 mmol) in 16 ml of THF was added thereto for 20 minutes, and the resulting solution was stirred for 8 hours. The reaction was ended by adding water, and the reaction mixture was extracted with ethyl acetate. Organic extract was dried with magnesium sulfate and concentrated under a reduced pressure. The concentrated residue was purified by column chromatography (EtOAc:MeOH=40:1) using silica gel (230 – 400 mesh), to obtain 88.0 mg of product (98% yield. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz): δ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(m, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03 (s, 3H), 1.37(t, J=7.14, 3H).

Example 5) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(1-cyano-2-ethoxycarbonyl-ethylidene)piperidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

120 mg of 60% NaH (3.01 mmol) was dissolved in 6 ml of purified tetrahydrofuran, and a solution of triethyl 3-cyano-3-(diethoxyphosphoryl)-propionic acid ethyl ester (791 mg, 3.01 mmol) in 0.5 ml of tetrahydrofuran was slowly added thereto. The resulting solution was then stirred for two and a half hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (300 mg, 0.86 mmol) was added to the above solution, and the resulting solution was stirred for 20 hours at room temperature. After adding water to the reaction mixture, the water layer was extracted with dichloromethane. Organic extract was dried with magnesium sulfate and concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol in ethyl acetate, to obtain 84.8 mg (22% yield)of the desired product as a solid.

$^1$H NMR ($CDCl_3$, 300MHz): $\delta$ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(m, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03 (s, 3H), 1.37(t, J=7.14, 3H).

Example 6) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-dicyanomethylidenepiperidinyl) phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl

acetamide (20.0 mg, 0.06 mmol) was dissolved in 1 ml of dichloromethane, and malononitrile (3.8 mg, 0.06 mmol) and $Al_2O_3$ (17.2 mg, Basic, I™, Aldrich) were added thereto. The resulting solution was stirred for 18 hours at 40°C, and then washed with water. The water layer was extracted with dichloromethane, and organic extract was dried with anhydrous magnesium sulfate, which was then filtered off. The filtrate was concentrated under a reduced pressure, to obtain 23.7 mg (99% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.47 (dd, J=14.0 Hz, 1.2 Hz, 1H), 7.09 (dd, J=8.7, 1.1 Hz, 1H), 6.92 (t, J=9.1 Hz, 1H), 6.31 (s, br, 1H), 4.77 (m, 1H), 3.99 (t, J=9.1 Hz, 1H), 3.76 (t, J=7.1Hz, 1H), 3.67 (m, 2H), 3.26 (t, J=5.5 Hz, 4H), 2.92 (t, J=5.4 Hz, 4H), 1.99 (s, 3H); IR (KBr, $cm^{-1}$): 3300, 2924, 2232, 1750, 1656, 1418, 1382, 1216, 866, 752.

Example 7) Preparation of N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-cyano)methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]2-oxo-5-oxazolidinyl]methyl-acetamide (2.42g, 6.93 mmol), ethyl cyanoacetate (6 ml, excess) and $Al_2O_3$ (2.08 g, 20.4 mmol, Basic, I™, Aldrich) were put into a reactor, and the resulting solution was then stirred for 24 hours at 90 – 100°C. The reaction mixture is filtered using cellite. The filtrate was washed with water and then extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate

and then concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 1.89g (61% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): $\delta$ 7.42 (dd, J=14.1 Hz, J=2.6 Hz, 1H), 7.04 (dd, J=8.8 Hz, J= 2.1 Hz, 1H), 6.89 (t, J=9.1 Hz, 1H), 6.68 (t, J=5.3 Hz, 1H), 4.76 (m, 1H), 4.27 (q, J=7.1 Hz, 2H), 4.00 (t, J=9.0Hz, 1H), 3.74 (m, 1H), 3.62 (m, 2H), 3.30-3.22 (m, 4H), 3.16 (t, J=5.5 Hz, 2H), 2.91 (t, J=5.7 Hz, 2H), 2.00 (s, 3H), 1.32 (t, J=7.1 Hz, 3H);

IR (KBr, $cm^{-1}$): 924, 2232, 1750, 1656, 1518, 1418, 1382, 1216, 866, 752.

Example 8) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-cyanomethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide salt thereof

80% NaH (12.9 mg, 0.43 mmol) was dissolved in 0.5 ml of purified tetrahydrofuran, and diethyl cyanomethyl phosphonate (55.7 mg, 0.32 mmol) was slowly added thereto. The resulting solution was stirred for one hour at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methylacetamide (100 mg, 0.29 mmol) was added to the above solution, which was then stirred for 3 hours at room temperature. Water was poured onto the reaction mixture, and water layer was then extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10%

methanol-ethyl acetate, to obtain 105 mg (64% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.47 (dd, J=14.1 Hz, J=2.55 Hz, 1H), 7.16 (dd, J=8.79, J=1.62 Hz, 1H), 6.94 (t, J=2.49 Hz, 1H), 6.23 (t, J=6.09 Hz, 1H), 5.12 (s, 1H), 4.78 (m, 1H), 4.16-4.00 (m, 1H), 3.79-3.72 (m, 1H), 3.69-3.58 (m, 2H), 3.20-3.10 (m, 4H), 2.78 (t, J=5.28 Hz, 2H), 2.54 (t, J=5.28 Hz, 2H), 2.00 (s, 3H);

$^{13}$C NMR (300MHz, $CDCl_3$): δ 171.91 (-$NHCOCH_3$), 164.45 (Ph, C-F), 157.01 (isoxazole carbonyl), 155.09 (piperidinyl C=), 114.65 (CN), 108.14 (H(CN)C=), 23.07 (-$NHCOCH_3$);

IR (KBr, $cm^{-1}$) 2232 (CN);

HRMS ($FAB^+$) $C_{19}H_{22}FN_4O_3$ calculated: 373.1598, found: 373.1676.

Example 9) Preparation of N-[[(5S)-3-[3-fluoro-4-((4-(3-thiophen-2-yl-5-isoxazolyl)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

80% NaH (17.2 mg, 0.57 mmol) was dissolved in 1.0 ml of purified tetrahydrofuran, and diethyl 3-(2-thiophenyl)-5-isoxazolmethylene phosphonate (129 mg, 0.43 mmol) was slowly added thereto. The resulting solution was stirred for one hour at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (100 mg, 0.29 mmol) was added to the above solution, which was then stirred for 20 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with

dicholoromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 42.4 mg (20% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.43 (dd, J=17.0, 13.5 Hz, 2H), 7.11 (t, J=3.5 Hz, 1H), 7.04 (d, J=9.0 Hz, 1H), 6.92 (t, J=8.8 Hz, 1H), 6.32 (t, J=7.2 Hz, 1H), 6.20 (s, 1H), 4.77 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.63 (m, 2H), 3.15 (m, 4H), 2.95 (t, J=4.5 Hz, 2H), 2.52 (t, J=4.5 Hz, 2H), 2.01 (s, 1H).

Example 10) Preparation of N-[[(5S)-3-[3-fluoro-4-((4-(3-(3-methyl-isothiazol-4-yl)-isoxazolyl)methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydro-chloride salt thereof

80% NaH (17.2 mg, 0.57 mmol) was dissolved in 1.0 ml of cleanly purified tetrahydrofuran, and 3-(2-isothiophenyl)-5-isoxazolmethylene phosphonate (136 mg, 0.43 mmol) was slowly added thereto. The resulting solution was stirred for one hour at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (100 mg, 0.29 mmol) was added to the above solution, which was then stirred for 20 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The

concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 31.9 mg (15% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.3 (dd, J=18.0 Hz, J=2.46 Hz, 1H), 7.07 (dd, J=18 Hz, J=1.8 Hz, 1H), 6.95 (s, 1H), 6.38 (t, J=6.1 Hz, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 4.77 (s, 1H), 4.07-3.98 (m, 1H), 3.79-3.71 (m, 1H), 3.69-3.52 (m, 2H), 3.18 (t, J=5.34 Hz, 4H), 2.99 (t, J=5.1 Hz, 2H), 2.60 (t, J=5.1 Hz, 2H), 2.01 (s, 3H).

Example 11) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-ethoxycarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

80% NaH (3.1 mg, 0.10 mmol) was dissolved in 1.0 ml of cleanly purified dimethoxyethane, and triethyl phosphonoacetate (2.1 ml, 0.10 mmol) was slowly added thereto. The resulting solution was stirred for 2 hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (30.0 mg, 0.09 mmol) was added to the above solution, which was then stirred for 2 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 23.2 mg

(64% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.42 (dd, J=12.0 Hz, J=3.0 Hz, 1H), 7.05 (dd, J=12.0 Hz, J=3.0 Hz, 1H), 6.92 (t, J=9.0 Hz, 1H), 6.47 (t, J=4.5 Hz, 1H), 5.71 (s, 1H), 4.78 (m, 1H), 4.17 (q, J=7.5 Hz, 2H), 3.78-3.60 (m, 5H), 3.11 (s, br, 4H), 2.49 (t, J=3.0 Hz, 2H), 2.01 (s, 3H), 1.39 (t, J=7.5 Hz, 3H).

Example 12) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-methylcarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

80% NaH (6.0 mg, 0.20 mmol) was dissolved in 1.0 ml of cleanly purified tetrahydrofuran, and diethoxy 2-oxopropylphosphonate (38.5 μl, 0.20 mmol) was slowly added thereto. The resulting solution was stirred for 2 and a half hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (57.5 mg, 0.17 mmol) was added to the above solution, which was then stirred for 3 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 58.5 mg (91% yield) of desired product of yellow color. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.41 (dd, J=14.2 Hz, 2.1 Hz, 1H), 7.03 (dd,

J=8.8 Hz, 2.6 Hz, 1H), 6.92 (t, J=9.1 Hz, 1H), 6.42 (t, J=6.0 Hz, 1H), 6.09 (s, 1H), 4.76 (m, 1H), 4.00 (m, 1H), 3.74 (dd, J=6.8 Hz, 2.4 Hz, 1H), 3.65 (m, 2H), 3.170-3.09 (m, overlap, 6H), 2.45 (t, *J*=5.1 Hz, 2H), 2.20 (s, 3H), 2.01 (s, 3H).

Example 13) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(1-ethoxycarbonylethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

80% NaH (6.0 mg, 0.20 mmol) was dissolved in 1.0 ml of cleanly purified dimethoxyethane, and triethyl 2-phosphonoacetate (43 μl, 0.20 mmol) was slowly added thereto. The resulting solution was stirred for 2 hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (50.0 mg, 0.14 mmol) was added to the above solution, which was then stirred for 20 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 9.2 mg (15% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.43 (d, J=14.1 Hz, 1H), 7.09-6.93 (m, 2H), 6.20 (t, J=2.97 Hz, 1H), 4.77 (m, 1H), 4.21 (q, J=14.3 Hz, 2H), 4.01 (t, J=8.79 Hz, 1H), 3.79-3.60 (m, 3H), 3.10 (s, br, 4H), 2.81 (s, br, 2H), 2.54 (s, br, 2H), 2.01 (s, 3H), 1.91 (s, 3H), 1.31 (t, J=14.3 Hz, 3H).

Example 14) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-carboxymethylidene piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and sodium salt thereof

14-1) Preparation of allyl diethoxyphosphonyl acetate

Diethyl phosphono acetic acid (1.0 g, 5.10 mmol) was dissolved in 5 ml of N,N-dimethylformamide, and potassium carbonate (1.06 g, 7.65 mmol) and allyl bromide (1.0 ml, 11.7 mmol) were added thereto. The resulting solution was stirred for one hour at 30-40°C, and then cooled down to room temperature. Water was poured to the mixture, and water layer was extracted with ethyl acetate. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was then concentrated under a reduced pressure. The residue was purified by column chromatography using 50% hexane-ethyl acetate to give 518 g (43%) of the desired product.

14-2) Preparation of (5S)-N-[3-[fluoro -4-(4-allyloxycarbonylmethylidene)piperidin-yl]phenyl]-2-oxo-5-oxazolidinyl]methylacetatamide

NaH 15.5 mg (80%, 0.52 mmol) was dissolved in 1 ml of clearly purified, allyl diethyoxyphosphonyl acetate 122 mg (0.52 mmol) was added thereto, and then the mixture was stirred at room temperature for 2 hours. To the reaction mixture, N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetatamide 50.0 mg (0.14 mmol) was added, and stirred at room temperature for 20 hours, and then refluxed for 3.5 hours. Water was added to the reaction

mixture, and the aqueous phase was extracted with dichloromethane. Organic extracts were dried with magnesium sulfate, and the magnesium sulfate was filtered off to give 110 mg (59%) of yellow desired product.

14-3) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-carboxymethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

(5S)-N-[3-[fluoro-4-(4-allyloxycarbonylmethylidene)piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (98 mg, 0.23 mmol), sodium 2-ethyl hexanoate (55.8 mg, 0.34 mmol), triphenyl phosphine (6.0 mg, 0.02 mmol) and tetrakis(triphenyl phosphine) palladium (0) (5.2 mg, 0.005 mmol) were dissolved in 1 ml of dichloromethane. The resulting solution was stirred for 20 hours at room temperature. Acetone was then added to the above solution to form solid, which was filtered and washed with ether, to obtain 55.8 mg (59% yield) of desired product as a white solid.

$^1$H NMR (300MHz, $CD_3OD$): $\delta$ 7.47 (dd, J=14.5 MHz, J=1.86 MHz, 1H), 7.12 (dd, J=8.79 MHz, J=1.14 MHz, 1H), 7.03 (t, J=9.09 MHz, 1H), 5.73 (s, 1H), 4.76 (m, 1H), 4.10 (t, J=9.06 MHz, 1H), 3.77 (dd, J=9.06 MHz, J=6.57 MHz, 1H), 3.54 (d, J=4.95 MHz, 2H), 3.06 (m, 4H), 2.95 (d, J=4.74 MHz, 2H), 2.38 (t, J=12.2 MHz, 2H), 1.95 (s, 3H).

Example 15) Preparation of N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-chloro)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and

hydrochloride salt thereof

80% NaH (7.2 mg, 0.24 mmol) was dissolved in 1.0 ml of purified tetrahydrofuran, and triethyl 2-chloro-2-phosphonoacetate (51.4 μl, 0.24 mmol) was slowly added thereto. The resulting solution was stirred for 1 and a half hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (60.0 mg, 0.17 mmol) was added to the above solution, which was then stirred for 4 hours at room temperature. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 30 mg (38% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.41 (d, J=14.2 Hz, 2.2 Hz, 1H), 7.03 (dd, J=8.8 Hz, 1.8Hz, 1H), 6.91 (t, J=9.2 Hz, 1H), 6.57 (t, J=6.0 Hz, 1H), 4.76 (m, 1H), 4.26 (q, J=7.1 Hz, 2H), 3.98 (t, J=6.2 Hz, 1H), 3.74 (t, J=8.8 Hz, 1H), 3.62 (m, 2H), 3.12 (m, 4H), 2.98 (t, J=5.5 Hz, 2H), 2.79 (t, J=5.5 Hz, 2H), 1.98 (s, 3H), 1.33 (t, J=7.1 Hz, 3H).

Example 16) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(1-cyanoethylidene)piperidinyl)- phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

80% NaH (7.4 mg, 0.246 mmol) was dissolved in 1.0 ml of cleanly purified tetrahydrofuran, and diethyl 2-cyanomethylphosphonoacetate (37 μl, 0.21 mmol) was slowly added thereto. The resulting solution was stirred for one and a half hours at room temperature. N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (60.0 mg, 0.17 mmol) was added to the above solution, which was then stirred for 20 hours at room temperature, and subsequently stirred 20 hours at 60°C. Water was poured onto the reaction mixture, and water layer was extracted with dicholoromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 21 mg (32% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.43 (d, J=14.2 Hz, 2.6 Hz, 1H), 7.05 (dd, J=8.8 Hz, 1.7 Hz, 1H), 6.91 (t, J=9.1 Hz, 1H), 6.40 (t, J=6.3 Hz, 1H), 4.77 (m, 1H), 4.00 (m, 1H), 3.76 (m, 1H), 3.64 (m, 2H), 3.12 (m, 4H), 2.77 (t, J=5.4 Hz, 2H), 2.54 (t, J=5.5 Hz, 2H), 2.00 (s, 3H), 1.93 (s, 3H).

Example 17) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methylacetamide and hydrochloride salt thereof

17-1) Preparation of N-(5S)-[3-[3-fluoro-4-(4-allyl-4-hydroxypiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetamide (100 mg, 0.29 mmol) was dissolved in 3 ml of tetrahydrofuran/water (v/v, 1/3), and indium (39.4 mg, 0.34 mmol) and allyl bromide (37 μl, 0.43 mmol) were added thereto. The resulting solution was stirred for 3 hours and then filtered, and the filtrate was extracted with dichloromethane. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 96.5 mg (86% yield) of white product.

17-2) Preparation of N-[(5S)-3-[3-fluoro-4-(2,3,4-trihydroxypropylidene)piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

N-(5S)-[3-[3-fluoro-4-(4-allyl-4-hydroxypiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (20 mg, 0.05 mmol), N-methylmorpholine N-oxide (50% aqueous solution, 19.2 mmol) and catalytic amount of osmium tetraoxide were added to 80% acetone, and the resulting solution was stirred for one hour at room temperature. Magnesium sulfate was added to the above solution, which was then stirred for 10 minutes, and solid was filtered. The filtrate was concentrated under a reduced pressure, to obtain 15.4 mg (68% yield) of yellow solid.

17-3) Preparation of N-[(5S)-3-[3-fluoro-4-(1-hydroxy-2-formylpropyl)piperidinyl]-phenyl-2-oxo-5-oxazolidinyl]methylacetamide

N-[(5S)-3-[3-fluoro-4-(1-hydroxy-2,3-dihydroxypropylidene)piperidinyl]-phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (1.38 g, 3.20 mmol) was dissolved

in 50% aqueous methanol solution, and sodium periodate (883 mg, 4.13 mmol) was added thereto. The resulting solution was stirred for one and a half hour at room temperature and then extracted with ethyl acetate several times. Organic extracts were collected and dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 612 mg (49% yield) of desired product.

17-4) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)- phenyl]-2-oxo-5-oxazolidinyl]methylacetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-hydroxy-4-(2-formyl)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (570 mg, 1.45 mmol) was dissolved in 10 ml of dichloromethane, and triethylamine (505 μl, 3.63 mmol) and 4-N,N-dimethylaminopyridine (354 mg, 2.90 mmol) were added thereto. The resulting solution was stirred for 10 minutes, and methanesulfonyl chloride (224 μl, 2.90 mmol) was slowly added thereto. The resulting solution was then stirred for 3 hours at 0°C and then washed with water, and water layer was extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate, which was filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography, to obtain 120 mg (22% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 10.0 (d, J=8.0 Hz, 1H), 7.45 (dd, J=14.1 Hz,

2.4 Hz, 1H), 7.07 (dd, J=8.7 Hz, 2.3 Hz, 1H), 6.95 (t, J=9.1 Hz, 1H), 6.19 (t, J=5.9 Hz, 1H), 5.93 (d, J=8.0Hz, 1H), 4.76 (m, 1H), 4.02 (t, J=8.9 Hz, 1H), 3.76 (t, J=6.7 Hz, 1H), 3.61 (m, 2H), 3.20 (m, 4H), 3.01 (t, J=5.7 Hz, 2H), 2.58 (t, J=5.5 Hz, 2H), 2.01 (s, 3H).

Example 18) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminoethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide]methylacetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (30 mg, 0.08 mmol) was dissolved in 1 ml of ethanol/water (v/v, 1/2), and sodium carbonate (5.1 mg, 0.05 mmol) and hydroxylamine hydrochloride salt (7.2 mg, 0.10 mmol) were added thereto. The resulting solution was stirred for 2 hours at 50°C. Water was poured onto the reaction mixture, and water layer was extracted with ethyl acetate. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 22 mg (71% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CD_3OD$): $\delta$ ppm 8.06 (d, J=10.4 Hz, 1H), 7.46 (dd, J=14.5 Hz, 2.5 Hz, 1H), 7.13 (dd, J=8.8 Hz, 2.3 Hz, 1H), 7.02 (t, J=9.1 Hz, 1H), 5.94 (d, J=10.4 Hz, 1H), 4.77 (m, 1H), 4.09 (t, J=9.1 Hz, 1H), 3.76 (m, 1H), 3.52 (d, J=7.3 Hz, 2H), 3.08 (m, 4H), 2.65 (t, J=5.4 Hz, 1H), 2.59 (t, J=5.5 Hz, 1H), 2.47 (m, 2H), 1.95 (s, 3H).

Example 19) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminoethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (30 mg, 0.08 mmol) was dissolved in 1 ml of ethanol/water (v/v, 1/2), and sodium carbonate (5.1 mg, 0.05 mmol) and methoxyamine hydrochloride salt (8.7 mg, 0.10 mmol) were added thereto. The resulting solution was stirred for 2 hours at 50°C. Water was poured onto the reaction mixture, and water layer was extracted with ethyl acetate. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 25.7 mg (80% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CD_3OD$): δ 8.08 (d, J=10.4 Hz, 1H), 7.46 (dd, J=14.3 Hz, 2.3 Hz, 1H), 7.13 (dd, J=8.9 Hz, 2.4 Hz, 1H), 7.02 (t, J=9.2 Hz, 1H), 5.90 (d, J=10.4 Hz, 1H), 4.77 (m, 1H), 4.079 (t, J=9.1 Hz, 1H), 3.80-3.74 (m, 4H), 3.55 (d, J=4.7 Hz, 2H), 3.09 (m, 4H), 2.65 (t, J=5.3 Hz, 1H), 2.59 (t, J=5.2 Hz, 1H), 2.47 (t, J=5.0 Hz, 2H), 2.00 (s, 3H).

Example 20) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminopropylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-(3-fluoro-4-(4-acetylethylidenepiperidinyl))-2-oxo-5-oxazolidinyl]-methylacetamide (40 mg, 0.10 mmol) was dissolved in 1 ml of ethanol/water (v/v, 1/2), and sodium carbonate (6.6 mg, 0.06 mmol) and hydroxyamine hydrochloride salt (9.30 mg, 0.13 mmol) were added thereto. The resulting solution was stirred for 2 hours at 50°C. Water was poured onto the reaction mixture, and water layer was extracted with ethyl acetate. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 17.8 mg (43% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.44 (dd, J=14.6 Hz, 1.1 Hz, 1H), 7.11 (dd, J=8.9 Hz, 1.7 Hz, 1H), 7.04 (m, 1H), 5.70 (s, 1H), 4.75 (m, 1H), 4.08 (t, J=8.9 Hz, 1H), 3.75 (dd, J=9.1 Hz, 6.5 Hz, 1H), 3.52 (m, 2H), 3.18 (t, J=5.5 Hz, 1H), 3.08 (t, J=11.8 Hz, 2H), 2.99 (t, J=5.7 Hz, 2H), 2.69 (t, J=5.5 Hz, 1H), 2.42 (m, 2H), 1.96 (s, 3H).

Example 21) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminopropylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-(3-fluoro-4-(4-acetylethylidenepiperidinyl))-2-oxo-5-oxazolidinyl]-methylacetamide (40 mg, 0.10 mmol) was dissolved in 2 ml of ethanol/water (v/v, 1/1), and potassium carbonate (14.2 mg, 0.10 mmol) and methoxyamine

hydrochloride salt (12.9 mg, 0.16 mmol) were added thereto. The resulting solution was stirred for 2 hours at 50°C. Water was poured onto the reaction mixture, and water layer was extracted with ethyl acetate. Organic extract was dried with magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 32.1 mg (74% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.45 (dd, J=14.5 Hz, 2.3 Hz, 1H), 7.23 (dd, J=5.5 Hz, 2.3 Hz, 1H), 7.04 (m, 1H), 5.65 (s, br, 1H), 4.75 (m, 1H), 4.08 (t, J=9.0 Hz, 1H), 3.76 (m, 4H), 3.55 (d, J=5.0 Hz, 2H), 3.18 (t, J=4.5 Hz, 1H), 3.04 (m, 4H), 2.74 (t, J=4.5 Hz, 2H), 2.42 (t, J=3.0 Hz, 2H), 1.91 (s, 3H).

Example 22) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)- phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-(3-fluoro-4-(4-acetylethylidenepiperidinyl))-2-oxo-5-oxazolidinyl]-methylacetamide (25 mg, 0.06 mmol) was dissolved in 2 ml of ethanol/water (v/v, 1/1), and sodium borohydridee (4.8 mg, 0.13 mmol) was added thereto. The resulting solution was stirred for 4 hours at room temperature, to which saturated aqueous ammonium chloride solution was then added, stirred again, and then extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 19.4 mg (77% yield) of white solid.

Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR (300MHz, $CDCl_3$): δ 7.39 (dd, J=14.2 Hz, 2.5 Hz, 1H), 7.03 (dd, J=8.8 Hz, 2.3 Hz, 1H), 6.90 (t, J=9.1 Hz, 1H), 6.50 (s, br, 1H), 5.28 (d, J=8.5 Hz, 1H), 4.75 (m, 1H), 4.63 (m, 1H), 3.99 (t, J=9.1 Hz, 1H), 3.75 (m, 1H), 3.63 (m, 2H), 3.02 (m, 4H), 2.47 (m, 2H), 2.34 (m, 2H), 2.00 (s, 3H), 1.29 (d, J=11.3 Hz, 3H).

Example 23) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-acetoxypropylidene)piperidinyl)- phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-[3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (30 mg, 0.08 mmol) was dissolved in 1 ml of dichloromethane, and pyridine (11 μl, 0.130 mmol) and purified acetyl chloride (9.2 μl, 0.13 mmol) were slowly added thereto. The resulting solution was stirred for 30 minutes while maintaining temperature at 0°C. The reaction mixture was washed with water, and water layer was extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 18.8 mg (57% yield) of yellow product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 7.39 (dd, J=14.0 Hz, 2.2 Hz, 1H), 7.03 (dd, J=8.6 Hz, 2.3 Hz, 1H), 6.92 (t, J=9.0 Hz, 1H), 6.41 (t, J=6.1 Hz, 1H), 5.62 (m, 1H),

5.22 (d, J=8.9 Hz, 1H), 4.75 (m, 1H), 4.00 (t, J=9.1 Hz, 1H), 3.73 (m, 1H), 3.63 (m, 2H), 3.04 (m, 4H), 2.54 (m, 1H), 2.45 (m, 1H), 2.34 (m, 2H), 2.03-2.01 (2s, 6H), 1.28 (d, J=6.4 Hz, 3H).

Example 24) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-(chloroacetoxy)propylidene)- piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-(3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)phenyl)-2-oxo-5-oxazolidinyl]methylacetamide (30 mg, 0.08 mmol) was dissolved in 1 ml of dichloromethane, and pyridine (11 μl, 0.13 mmol) and purified chloroacetyl chloride (10 μl, 0.13 mmol) were slowly added thereto. The resulting solution was stirred for 30 minutes while maintaining the temperature at 0°C. The reaction mixture was washed with water, and water layer was extracted with ethyl acetate. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 25.1 mg (70% yield) of yellow product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 7.39 (dd, J=14.3 Hz, 2.4 Hz, 1H), 7.02 (dd, J=8.9 Hz, 2.3 Hz, 1H), 6.89 (t, J=9.0 Hz, 1H), 5.70 (m, 1H), 5.21 (d, J=9.1 Hz, 1H), 7.45 (m, 1H), 4.02-3.96 (m, 3H), 3.74 (t, J=9.0 Hz, 1H), 3.62 (m, 2H), 3.10-3.06 (m, 2H), 3.06-2.99 (m, 2H), 2.57 (m, 1H), 2.43 (m, 1H), 2.35 (m, 2H), 2.01 (s, 3H), 1.33 (d, J=6.3 Hz, 3H).

Example 25) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(2-(dichloroacetoxy)propylidene)-piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide and hydrochloride salt thereof

N-[(5S)-3-(3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)phenyl)-2-oxo-5-oxazolidinyl]methylacetamide (30 mg, 0.08 mmol) was dissolved in 1 ml of dichloromethane, and pyridine (11 μl, 0.13 mmol) and purified dichloroacetyl chloride (13 μl, 0.13 mmol) were slowly added thereto. The resulting solution was stirred for 30 minutes while maintaining the temperature at 0°C. The reaction mixture was washed with water, and water layer was extracted with ethyl acetate. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure, to obtain 26.4 mg (69% yield) of yellow product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 7.40 (dd, J=14.1 Hz, 2.5 Hz, 1H), 7.02 (dd, J=8.8 Hz, 2.0 Hz, 1H), 6.54 (t, J=5.9 Hz, 1H), 5.90 (s, 1H), 5.72 (m, 1H), 5.26 (d, J=8.9 Hz, 1H), 4.76 (m, 1H), 4.00 (t, J=9.1 Hz, 1H), 3.74 (m, 1H), 3.62 (m, 2H), 3.11 (m, 2H), 2.97 (m, 2H), 2.56 (m, 1H), 2.49-2.32 (m, 3H), 2.02 (s, 3H), 1.38 (d, J=6.4 Hz, 3H).

Example 26) Preparation of N-[[(5S)-3-[3-fluoro-4-(4-(cyanomethylidene) piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide and hydrochloride salt thereof

N-[[(5S)-3-[3-fluoro-4-(4-cyanomethylidenepiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (30 mg, 0.08 mmol) was dissolved in 2 ml of 1,4-dioxane, and Lawesson's reagent (35 mg, 0.08 mmol) was added thereto. The resulting solution was stirred for 18 hours at 100°C. The reaction mixture was washed with water, and water layer was extracted with dichloromethane. Organic extract was dried with anhydrous magnesium sulfate, which was then filtered off, and the filtrate was concentrated under a reduced pressure. The concentrated residue was purified by column chromatography using 10% methanol-ethyl acetate, to obtain 18.3 mg (52% yield) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 8.39 (s, br, 1H), 7.45 (d, J=13.5 Hz, 1H), 7.05 (s, br, 2H), 5.21 (s, 1H), 4.99 (m, 1H), 4.21-4.18 (m, 1H), 4.13-4.04 (m, 2H), 3.84 (t, J=9.2 Hz, 1H), 3.23-3.16 (m, 4H), 2.81 (t, J=5.4 Hz, 2H), 2.59 (s, 5H).

Example 27) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-3-aminopropyl idene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide and hydrochloride salt thereof

27-1) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-2-ethoxycarbonylethyl idene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

NaH 7.4 mg (60%, 0.25 mmol) was dissolved in 6 ml of clearly purified,

triethyl 3-cyano-3-(diethyoxyphosphoryl)propionic acid ethyl ester 0.5 ml of in tetrahydrofuran was added thereto, and then the mixture was stirred at room temperature for 2.5 hours. To the reaction mixture, N-[(5S)-3-[3-fluoro-4-(4-oxopiperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetatamide 300 mg (0.86 mmol) was added, and stirred at room temperature for 20 hours. Water was added to the reaction mixture, and the aqueous phase was extracted with dichloromethane. Organic extracts were dried with magnesium sulfate, and concentrated under a reduced pressure. The residue was purified by column chromatography using 10% methanol-ethyl acetate to give 84.8 mg (22%) of desired product.

27-2) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-hydroxybutylidene) piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

(5S)-N-[3-fluoro-4-(4-(1-cyano-2-ethoxycarbonylethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (48 mg, 0.11 mmol) was dissolved in 3 ml of tetrahydrofuran/water mixture (1/2), and sodium borohydride 10 mg (0.11 mmol) was added to the reaction mixture. The resulting mixture was stirred at 0°C for 3 hours and then stirred at room temperature for 16 hours. Saturated ammonium chloride solution was added to the reaction mixture, which was then stirred for 5 minutes. Aqueous phase was extracted with ethyl acetate, and organic phase was dried with magnesium sulfate, and then concentrated under a reduced pressure to give 38.9 mg (89% yield) of desired product as a yellow solid.

27-3) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-methansulfonyloxy)

butylidene)piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-hydroxybutylidene) piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide 38.9 mg (0.09 mmol) and triethylamine 48 μl (0.35 mmol) were dissolved in 1 ml of dichloromethane, and methansulfonyl chloride 21 μl (0.27 mmol) was added thereto, and then the resulting mixture was siirred for 2 hours. The reaction mixture was washed with water, and aqueous phase was extracted with dichloromethane. Organic phase was dried with magnesium sulfate, and concentrated under a reduced pressure to give 46 mg (99% yield) of desired product.

27-4) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-azido)butylidene) iperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-methansulfonyloxy)butylidene)-piperidinyl]phenyl]--oxo-5-oxazolidinyl]methylacetamide 46 mg (0.09 mmol) was dissolved in 1 ml of N,N-dimethylformamide, and sodium azide 48 mg (0.74 mmol) was added thereto. The resulting mixture was stirred at 80°C for 18 hours. Water was added to the reaction mixture, and the aqueous phase was extracted with ethyl acetate. Organic extracts were dried with magnesium sulfate, and concentrated under a reduced pressure, to give 33.3 mg (81%) of desired product.

27-5) Preparation of N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-3-aminopropylidene) iperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

N-[(5S)-3-[3-fluoro-4-(4-(1-cyano-4-azido)butylidene) iperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide 33.3 mg (0.08 mmol) was dissolved in 3 ml of tetrahydrofuran/water mixture (1/2), and indium 35 mg (0.30 mmol) and 290 μl of 6N hydrochloric acid were added to the reaction mixture. The resulting mixture was stirred at room temperature for 10 hours. The reaction mixture was filtered under a reduced pressure, and filtrate was washed with ethyl acetate several times. Aqueous phase was then neutralized with 3N aqueous sodium hydroxide and extracted with ethyl acetate. Organic extract was dried with magnesium sulfate, and then concentrated under a reduced pressure to give 13.0 mg (41%) of desired product. Hydrochloride salt was obtained by treating the product with ethyl ether saturated with hydrogen chloride gas.

$^1$H NMR ($CDCl_3$, 300MHz,): δ 7.41 (dd, J=14.0, 2.4 Hz, 1H), 7.02 (d, J=8.8 Hz, 1H), 6.89 (t, J=9.2 Hz, 1H), 6.73 (s, br, 1H), 4.74 (m, 1H), 4.98 (t, J=8.9 Hz, 1H), 3.75 (t, J=9.2 Hz, 1H), 3.62 (t, J=5.5 Hz, 2H), 3.49 (t, J=6.6 Hz, 2H), 3.11 (m, 4H), 2.79 (t, J=5.9 Hz, 2H), 2.63-2.51 (m, 4H), 1.96 (s, 3H)

**Anti-microbial activity test *in vitro***: Srains were cultivated for 18 hours at 37°C in Agar Dilution method using Mueller Hinton Agar, and then plane plates inoculated with the strains by diluting them two times gradually were aligned in a row. Minimum inhibition concentrations (MIC, μg/ml) for the representative compounds of the present invention were decided through visual observation, and the results are shown in the following table 2.

Table 2) Results of Testing Anti-microbial Activities (MIC, μg/ml)

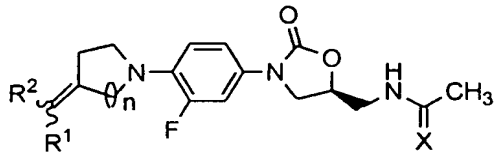
| Compd. Nos. / Micro-organism | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. aureus ATCC 29213 | 2 | 4 | 2 | 32 | 16 | 16 | 8 | 16 | 8 | 32 | 2 | 8 |
| MRSA C2207 | 4 | 4 | 2 | 32 | 16 | 8 | 8 | 16 | 8 | 16 | 2 | 4 |
| MRSA C5100 | 4 | 4 | 2 | 16 | 8 | 8 | 8 | 8 | 4 | 16 | 2 | 4 |
| MRSA C6068 | 2 | 4 | 1 | 16 | 8 | 8 | 16 | 8 | 4 | 16 | 2 | 4 |
| CRSA C6043 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 8 | 8 | 16 | 2 | 4 |
| CRSA C1062 | 4 | 4 | 2 | 32 | 16 | 8 | 8 | 16 | 16 | 16 | 2 | 8 |
| MSSA C7142 | 4 | 4 | 2 | 32 | 8 | 16 | 16 | 8 | 8 | 8 | 2 | 4 |
| MSSA C2214 | 4 | 4 | 4 | 16 | 16 | 16 | 16 | 16 | 8 | 8 | 2 | 8 |
| S. epidermis ATCC12228 | 1 | 1 | 0.5 | 4 | 2 | 2 | 1 | 4 | 1 | 2 | 0.5 | 1 |
| S. epidermis C2230 | 2 | 2 | 2 | 8 | 4 | 8 | 8 | 16 | 4 | 4 | 2 | 2 |
| S. epidermis C2235 | 2 | 2 | 1 | 8 | 4 | 4 | 8 | 8 | 1 | 4 | 2 | 2 |
| E. faecalis ATCC29212 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 16 | 8 | 8 | 2 | 16 |
| E. faecalis C6288 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 16 | 4 | 8 | 2 | 4 |
| E. faecalis C6291 | 4 | 4 | 2 | 16 | 8 | 8 | 16 | 8 | 8 | 4 | 2 | 8 |
| E. faecium C2252 | 4 | 4 | 2 | 16 | 8 | 8 | 8 | 8 | 8 | 4 | 2 | 8 |
| E. faecium C6301 | 2 | 2 | 2 | 16 | 8 | 8 | 8 | 8 | 4 | 2 | 2 | 4 |
| S. pyogenes ATCC8668 | 1 | 1 | 0.5 | 2 | 2 | 2 | 8 | 8 | 4 | 2 | 2 | 2 |
| S. pyogenes C6003 | 4 | 4 | 2 | 16 | 8 | 8 | 0.2(5) | 4 | 2 | 2 | 0.5 | 8 |
| S. pyogenes C6012 | 1 | 1 | 0.5 | 4 | 2 | 2 | 16 | 16 | 8 | 8 | 2 | 1 |
| VRE C6487 | 4 | 2 | 4 | 16 | 4 | 8 | 2 | 1 | 1 | 2 | 0.5 | 8 |
| VRE C6488 | 2 | 2 | 4 | 16 | 8 | 8 | 8 | 8 | 8 | 4 | 1 | 8 |

Table 3) Results of Testing Anti-microbial Activities (MIC, μg/ml)

| Compd. Nos. / Strain | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | LZD | VAN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. aureus ATCC29213 | 8 | 8 | 8 | 16 | 8 | 16 | 16 | 16 | 2 | 2 | 4 | 1 |
| MRSA C2207 | 8 | 4 | 8 | 16 | 16 | 8 | 16 | 16 | 2 | 2 | 4 | 1 |
| MRSA C5100 | 4 | 4 | 8 | 8 | 8 | 16 | 16 | 8 | 1 | 1 | 2 | 2 |
| MRSA C6068 | 4 | 4 | 4 | 8 | 4 | 8 | 8 | 8 | 2 | 2 | 2 | 1 |
| CRSA C6043 | 8 | 4 | 8 | 16 | 8 | 16 | 16 | 16 | 2 | 2 | 2 | 2 |
| CRSA C1062 | 8 | 4 | 8 | 32 | 16 | 16 | 8 | 16 | 2 | 2 | 4 | 2 |
| MSSA C7142 | 8 | 4 | 16 | 16 | 16 | 16 | 16 | 16 | 2 | 2 | 4 | 2 |
| MSSA C2214 | 8 | 8 | 8 | 16 | 16 | 16 | 16 | 16 | 2 | 2 | 4 | 1 |
| S. epidermidis ATCC12228 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 0.5 | 0.5 | 0.5 | 1 |
| S. epidermidis C2230 | 4 | 4 | 4 | 16 | 4 | 8 | 8 | 8 | 1 | 1 | 2 | 2 |
| S. epidermidis C2235 | 4 | 2 | 4 | 8 | 4 | 8 | 8 | 8 | 0.5 | 0.5 | 2 | 2 |
| E. faecalis ATCC29212 | 8 | 4 | 8 | 16 | 8 | 8 | 8 | 8 | 2 | 2 | 4 | 4 |
| E. faecalis C6288 | 4 | 2 | 4 | 8 | 4 | 8 | 16 | 8 | 1 | 1 | 2 | 2 |
| E. faecalis C6291 | 4 | 4 | 4 | 8 | 8 | 8 | 16 | 8 | 1 | 1 | 2 | 2 |
| E. faecium C2252 | 4 | 4 | 4 | 8 | 4 | 8 | 16 | 8 | 1 | 1 | 2 | 1 |
| E. faecium C6301 | 4 | 4 | 4 | 8 | 4 | 8 | 8 | 8 | 1 | 1 | 2 | 1 |
| S. pyogenes ATCC8668 | 2 | 1 | 1 | 2 | 2 | 0.5 | 2 | 2 | 0.5 | 0.5 | 0.5 | 0.12 |
| S. pyogenes C6003 | 4 | 2 | 4 | 8 | 8 | 8 | 8 | 8 | 0.25 | 0.25 | 2 | 4 |
| S. pyogenes C6012 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 0.25 | 0.25 | 0.5 | 0.5 |
| VRE C6487 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 0.5 | 0.5 | 2 | >32 |
| VRE C6488 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 0.5 | 0.5 | 2 | >32 |

What is claimed is:

1. A methylidene oxazolidinone compound represented by the following formula (I) or a pharmaceutically acceptable salt thereof:



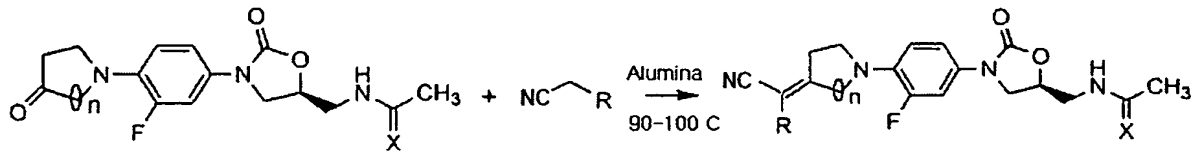
n=1, 2

(I)

wherein X represents an oxygen or sulfur atom; and

$R^1$ and $R^2$ independently represent hydrogen atom, cyano group, alkyl group, halogen atom, acetoxy group, ethoxycarbonyl group, hydroxy group, hydroxyimino group, methoxyimino group or aminoethyl group, or a unsaturated 5-membered heterocyclic substituent containing one or more hetero atoms selected from the group consisting of oxygen, nitrogen and sulfur.

2. A method for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (III):



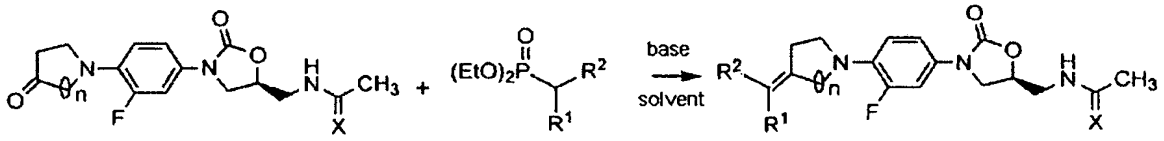

n = 1,2 X = O or S n = 1,2 X = O or S

(II) (III) (I)

wherein the compound of formula (III) is preferably malonitrile, ethylcyano or acetate group. Knoevenagel Condensation to be used in this method is carried

out without or with a solvent selected from methylene chloride and benzene, aluminum oxide, amine or the like can be used as a catalyst, and reaction temperature is preferable in the range of 90-100°C. In the above formula, each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

3. A method for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (IV):

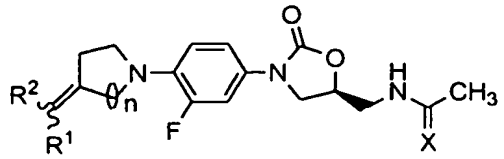



n = 1,2 X = O or S n = 1,2 X = O or S

(II) (IV) (I)

wherein various derivatives represented by formula (IV) can be used. Firstly, it is necessary to activate the compound (IV). That is, by using tetrahydrofuran, dimethylethane, dimethyl formanide or the like as a solvent, and using sodium hydride, potassium t-butoxide or the like as a base, phophonate is activated, and then Wadwards-Horner-Emmons reaction is carried out after adding the compound (II). It is possible to react in the temperature range of 40-100°C, but preferable temperature is 25°C. In the above formula, each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

4. The compound of claim 1, represented by the following formula (I):




n=1, 2

(I)

wherein each of n, R, $R^1$ and $R^2$ is the same as defined in claim 1.

5. The compound of claim 4, wherein n is 1.

6. The compound of claim 5, wherein n is 1, including N-[[(5S)-3-[3-fluoro-4-(3-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((3-(1-ethoxycarbonyl-1-cyano)methylidene)pyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,N-[[(5S)-3-[3-fluoro-4-(3-cyano-methylidenepyrrolidin-1-yl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((3-(1-methyl-1-cyano)methylidene)pyrrolidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, or a hydro-chloride salt thereof.

7. The compound of claim 4, wherein n is 2.

8. The compound of claim 7, wherein n is 2, including N-[[(5S)-3-[3-fluoro-4-(4-(1-cyano-2-ethoxy-carbonylethylidene)piperidin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[(5S)-3-[3-fluoro-4-(4-dicyanomethylidenepyrrolidin-1-yl)phenyl]-2-oxo-5-oxazol-idinyl]methylacetamide, N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-cyano)-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-cyanomethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(3-thiophen-2-yl-5-isoxazolyl)methylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(3-(3-methyl-isothiazol-4-yl)-iso-xazolyl)methylidene)piperidinyl)phenyl]-2-oxo-

5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-ethoxycarbonyl-methylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-methylcarbonylmethylidene-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(1-ethoxycarbonylethylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-carboxymethylidenepiperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-((4-(1-ethoxycarbonyl-1-chloro)methylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(1-cyanoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-oxoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminoethylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyiminoethylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxyiminopropylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-methoxyimino-propyl-idene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-hydroxypropylidene)piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-acetoxypropylidene)piperidinyl)- phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-(chloroacetoxy)-propylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]- acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(2-(dichloroacetoxy)propylidene)piperidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, N-[[(5S)-3-[3-fluoro-4-(4-(cyano-methylidene)-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]thioacetamide, or a hydro-chloride salt thereof.

9. The compound according to claim 1, wherein the pharmaceutically acceptable salt is a methanesulfonate, fumarate, hydrobromide salt, citrate, maleate, phosphate, sulfate, hydrochloride salt or a sodium salt.

K2784
F172

# 발 명 신 고 서

| | | | | | | |
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| | 영 문 | New Oxazolidinone Derivatives Having Methylidene Pyperidinyl Moiety and the Preparation Thereof | | | | |
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| 비 고 | | | | | | |

위와 같이 발명을 신고하오니 승계하여 주시기 바랍니다.

붙 임 : 1. 발명명세서
2. 양도증
3. 특허활용 추진의견서

2002. 2. 26.

한국과학기술연구원장 귀하

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다음의 발명에 관하여 국내 및 국외에서 특허를 받을 수 있는 권리를 귀하에게 양도함.

다 음

| | | |
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| | | 영문 | Lee, Jae Seok | | |
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| | 성명 | 국문 | 김 학 수 | 주민등록번호 | 740606-1531117 |
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| | | 영문 | Kim, Sang Hee | | |

[첨부 2]

# 명세서

## 1. 발명의 명칭

새로운 메틸리덴 피페리디닐 옥사졸리디논 유도체 및 그 제조방법

## 2. 도면의 간단한 설명

도면1은 본 발명의 대표적인 화합물구조이다. 도면 2과 3은 화합물 (I)을 합성하는 제조공정이다.

## 3. 발명의 상세한 설명

### 3.1 발명이 속하는 기술분야

사회생활이 다양화되고 복잡해지면서 일반인들의 세균 감염 기회가 많아졌으며, 병원에서 감염증을 치료하기 위한 고단위 항생제의 사용, 따라서 항생제 오용 및 남용문제로 인한 다양한 내성균주들이 신속히 증가되었기 때문이다. 현재 세계적으로 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 메티실린 저항성 스태필로코커스 에피더미스(MRSE), 엔테로코커스 뉴모니에(Enterococcus pneumoniae), 퀴놀론 저항성 스태필로코커스 아우레우스(QRSA), 벤코마이신 저항성 엔테로 콕사이(VRE), 그리고 다제내성 마이코 박테리움 튜베르큐로시스(Mycobacterium tuberculosis)와 같은 균주들이 이미 사용중인 대부분의 항생제에 대해 내성을 나타내고 있다. 현재 이런 내성문제에 대해서는 새로운 구조와 새로운 기전을 갖는 항생제를 연구 개발이 절실히 요구되고 있다.

### 3.2 그 분야의 종래기술 및 문제점

옥사졸리디논 계열 항생제는 1987년 Dupont사에서 Dup-721의 약효 검색결과 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 베타락타마제에 대해 활성을 보여 이 계열의 화합물이 항균활성을 지닌다는 사실을 밝혔다. 그러나 Dup-721은 임상 I 단계에서 독성문제가 발생되어 개발이 중단되었다. 그 이후 이 계열 화합물 구조, 활성 연구가 Pharmacia Upjohn, Merck, Bayer등사에서 계속 진행되어왔다. 2000년 4월 Upjohn사에서는 새로운 골격을 갖는 항생제인 리네졸리드(linezolid)를 개발하였고 이 화합물은 지복스(Zyvox)라는 상품명으로 시판하게 되었고, 이것은 35년 만에 처음으로 선을 보인 새로운 유형의 항생제에 해당한다. 그러나 이 화합물은 좋은 pharmacokinetic profile(약동력학적 성질)을 보이지만 MRSA 나 VRE와 같은 균주에 활성이 높은 것은 아

니다. 따라서 활성이 우수한 신규 화합물의 개발이 필요하다.

3.3 발명이 이루고자 하는 기술적 과제 (발명의 목적)

본 발명은 이와 같은 다제 내성균주에 효능이 높은 항균제로서의 가능성이 있는 화합물과 그의 합성방법에 관한 것이다. 본 화합물의 항균 활성은 대조화합물로서 Upjohn사의 리네졸리드에 비해서 선택된 MRSA, VRE 및 그람양성균주에 대해서 2배 정도 좋은 항균 활성을 보이고 있다. 본 발명에서는 현재 세계적으로 문제가 되고있는 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 메티실린 저항성 스태필로코커스 에피더미스(MRSE), 엔테로코커스 뉴모니에(Enterococcus pneumoniae), 퀴놀론 저항성 스태필로코커스 아우레우스(QRSA), 벤코마이신 저항성 엔테로 콕사이(VRE)등에 좋은 항균력을 가진 화합물을 합성하고자 하였다.

3.4 발명의 구성 및 작용

본 발명은 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 메티실린 저항성 스태필로코커스 에피더미스(MRSE), 엔테로코커스 뉴모니에(Enterococcus pneumoniae), 퀴놀론저항성 스태필로코커스 아우레우스(QRSA), 벤코마이신 저항성 엔테로 콕사이(VRE)등에 좋은 항균력을 가진 화합물을 합성하는 방법과 합성된 화합물의 생리활성 시험결과로 구성되어있다.

3.5 발명의 효과

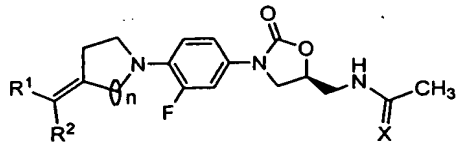
본 발명에 의해 합성된 화합물들은 기존 항생제에 내성을 보이는 균주를 효과적으로 생리활성을 보이는 것을 생체 외 실험에서 증명하였다. 이는 기존의 항생제로 치료할 수 없는 병원균을 치료할 수 있는 아주 획기적인 연구 결과라고 할 수 있다.

본 발명의 옥사졸리디논 계열의 화합물들은 현재 임상에서 사용되는 항생제와는 달리 간단한 화학적 구조를 갖고 있으며 병원균의 단백질 합성의 초기단계에서 억제작용을 한다.

## 4. 특허청구범위

6.1 청구항 1

[제 1항] 다음 일반식 (I)로 표시되는 메틸리덴 피페리디닐 옥사졸리디논 유도체 및 약제학적으로 허용되는 염



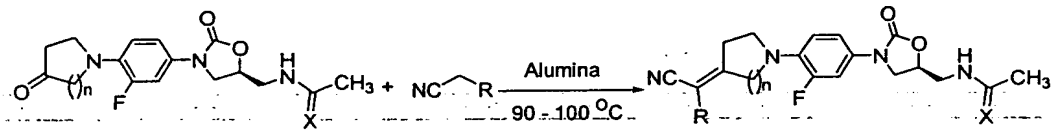
n = 1, 2

(I)

상기 식 중 X는 산소 황 원자를 나타내고, n은 1 또는 2를 표시하며, $R^1$과 $R^2$는 수소, 시아노기, 알킬 할로겐, 아세톡시, 에틸카르보닐, 아세톡시, 알코올, 아민, 헤테로고리 치환체를 나타낸다. 알킬 치환체로는 메틸, 에틸, 프로필기를 말하고, 할로겐으로는 브로모, 클로로를 말한다. 아세톡시는 모노클로린, 다이클로린으로 치환된 구조를 말한다. 옥심은 하이드록시옥심과 메톡시옥심을 말한다. 헤테로고리 치환체는 불포화된 5환 헤테로고리를 말하며, 헤테로고리에는 산소, 질소, 황 원자를 적어도 한 개 이상 포함하고 있는 구조를 말한다. 이러한 예로는 이소옥사졸, 티오펜, 이소티아졸, 티아졸, 티아디아졸등을 말한다.

6.2 청구항 2

[제 2 항] 일반식 (II)의 화합물과 일반식 (III)의 화합물을 반응시켜 얻는 것이 특징인 일반식 (I) 화합물의 제조 방법




n = 1, 2 X = O or S

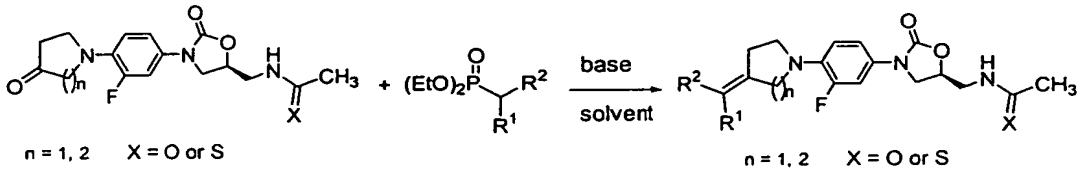
n = 1, 2 X = O or S

(II) (III) (I)

상기에서는 일반식 (III)으로 표시된 화합물은 말로노나이트릴과 에틸 시아노기, 아세테이트기가 적당하다. 여기서 이용되는 Knoevenagel Condensation방법은 메틸렌 클로리드, 벤젠등 용매 혹은 무용매하에서 진행되며, 촉매로는 알루미늄 옥사이드, 아민등 가능하며, 반응 온도는 90-100 °C 가 적당하다.
상기 식에서 n, R, $R^1$, $R^2$ 는 각각 제1항에서 정의한 것과 동일하다.

6.3 청구항 3

[제 3 항] ] 일반식 (II)의 화합물과 일반식 (IV)의 화합물을 반응시켜 얻는 것이 특징인 일반식 (I) 화합물의 제조 방법



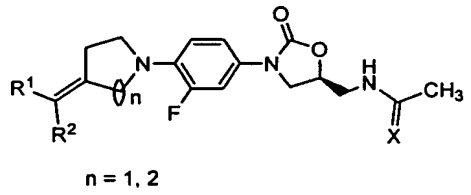

(II) (IV) (I)

상기에서는 일반식 (IV)로 표시되는 다양한 유도체가 가능하며, 우선 화합물 (IV)를 활성화해야만 한다. 즉 용매는 테트라히드로퓨란, 디메틸에탄, 디메틸포름아미드등을 사용하며, 염기로서는 소듐 히드리드, 삼차-부톡사이드 포타슘 염를 사용하여 포스포네이트를 활성화한 후 화합물 (II)를 넣어서 Wadwards-Horner-Emmons 반응을 실행한다. 이때 반응 온도는 40 ~ 100 ℃가 가능하나 25 ℃가 적당하다.

상기식에서 n, R, $R^1$, $R^2$는 각각 제1항에서 정의한 것과 동일하다.

6.4 청구항 4

[제 4 항] 청구1항에서 다음의 화학식을 가지는 화합물




상기 식에서 n, X, R, $R^1$, $R^2$는 각각 제1항에서 정의한 것과 동일하다.

6.5 청구항 5

[제 5 항] 청구 4항에서 n이 1인 화합물

6.6 청구항 6

[제 6 항] 청구 5항에서 n이 1인 화합물은 다음과 같다.

N-[(5S)-3-[3-플루오로-4-(3-디시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;

N-[(5S)-3-[3-플루오로-4-(3-(1-시아노-1-에톡시카보닐)메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(3-시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염;
N-[(5S)-3-[3-플루오로-4-(3-에톡시카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(3-메틸카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;

6.7 청구항 7

[제 7 항] 청구 4항에서 n이 2인 화합물

6.8 청구항 8

[제 8 항] 청구 7항에서 n이 2인 화합물은 다음과 같다.
N-[(5S)-3-[3-플루오로-4-(4-디시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(1-시아노-1-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염;
N-[(5S)-3-[3-플루오로-4-(4-(3-(2-티오펜닐)-5-이소옥사졸릴메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(3-(3-메틸-4-이소티아졸릴)-5-이소옥사졸릴)메틸리덴)피페리디닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-메틸카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-카복시메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 나트륨 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-클로로-1-에톡시카보닐메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-시아노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;

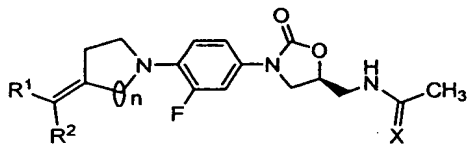
N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-하이드록시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-디클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(시아노메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-3-아미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염;

6.9 청구항 9

[제 9 항] 이 화합물은 약제학적으로 허용된 염을 포함한다. 즉 메탄설폰산 염, 퓨마렌산 염, 브롬산 염, 시트릭산 염, 말레인산 염, 인산 염, 환산 염, 염산 염, 소듐의 형태 또는 염이 아닌 아민 상태를 포함한다.

## 5. 도면

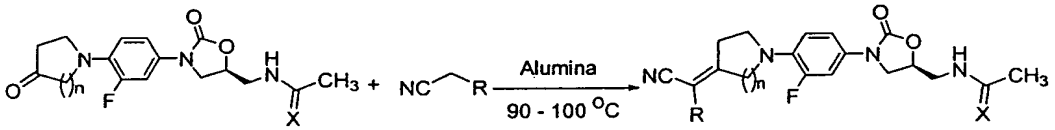
### 도면 1



n = 1, 2

(I)

### 도면 2

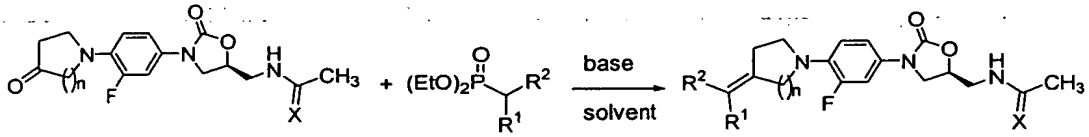


n = 1, 2 X = O or S

n = 1, 2 X = O or S

(II) (III) (I)

### 도면 3



n = 1, 2 X = O or S

n = 1, 2 X = O or S

(II) (IV) (I)

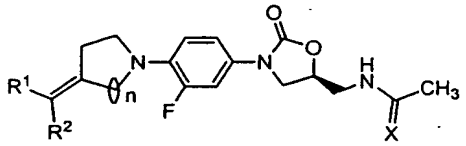
[명 세 서]

[발명의 명칭]

새로운 메틸리덴 피페리디닐 옥사졸리디논 유도체 및 그 제조방법

[발명의 상세한 설명]

본 발명은 MRSA (메티실린 저항성 스태필러코커스 아우레우스) 및 VRE (Vancomycin-resistant Enterococci) 등 내성균주를 포함한 그람양성균에 항균력을 지닌 일반식 (I)의 구조로 표시되는 옥사졸리디논계 화합물과 그 염 및 그의 제조방법에 관한 것이다.




n = 1, 2

(I)

상기 식 중 X는 산소, 황을 나타내고, n은 1 또는 2를 표시하며, $R^1$과 $R^2$는 수소, 시아노기, 알킬, 할로겐, 아세톡시, 에톡시카보닐, 히드록시이미노, 메톡시이미노, 히드록시, 아미노에틸, 헤테로고리 치환체를 나타낸다. 알킬 치환체는 메틸, 에틸, 프로필기등을 말하고, 할로겐은 브로모, 클로로기를 말한다. 아세톡시는 모노클로로, 다이클로로등으로 치환된 구조를 말한다. 헤테로고리 치환체는 불포화된 5환 헤테로고리를 말하며, 헤테로고리에는 산소, 질소, 황 원자를 적어도 한 개 이상 포함하고 있는 구조를 말한다. 이러한 예로는 이소옥사졸, 티오펜, 티아졸, 이소티아졸 등을 말한다. 이 화합물은 약제학적으로 허용된 염을 포함한다. 즉 메탄설폰산 염, 퓨마렌산 염, 브롬산염, 시트릭산 염, 말레인산 염, 인산 염, 황산 염, 염산 염, 소듐 염의 형태 또는 염이 아닌 중성 아민 상태를 포함한다.

2차 대전 이후 항생제에 관한 연구는 많이 진행 되어왔다. 이들 항생제의 화학구조를 보면 베타 락탐계, 아미노글루코사이드, 마크로리이드, 퀴놀론, 테트라사이클린, 글리코 펩타이드등 계열로 구분 할 수 있다. 이러한 항생제들은 현재에 항생제가 내성균의 발현으로 인해 무능화되는 추세가 심각해지고 있다.
이것은 사회생활이 다양화되고 복잡해지면서 일반인들의 세균 감염 기회가 많아졌

으며, 병원에서 감염증을 치료하기 위한 고단위 항생제의 사용, 따라서 항생제 오용 및 남용문제로 인한 다양한 내성균주들이 신속히 증가되었기 때문이다. 현재 세계적으로 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 메티실린 저항성 스태필로코커스 에피더미스(MRSE), 엔테로코커스뉴모니에(Enterococcus pneumoniae), 퀴놀론 저항성 스태필로코커스 아우레우스(QRSA), 벤코마이신 저항성 엔테로 콕사이(VRE), 그리고 다제내성 마이코 박테리움 튜베르큐로시스(Mycobacterium tuberculosis)와 같은 균주들이 이미 사용중인 대부분의 항생제에 대해 내성을 나타내고 있다. 현재 이런 내성문제에 대해서는 새로운 구조와 새로운 기전을 갖는 항생제의 연구 개발이 절실히 요구되고 있다.

옥사졸리디논 계열 항생제는 1987년 Dupont사에서 Dup-721의 약효 검색결과 메티실린 저항성 스태필로코커스 아우레우스(MRSA), 베타락타마제에 대해 활성을 보여 이 계열의 화합물이 항균활성을 지닌다는 사실을 밝혔다. 그러나 Dup-721은 임상 I 단계에서 독성문제가 발생되어 개발이 중단되었다. 그 이후 이 계열 화합물 구조, 활성 연구가 Pharmacia Upjohn, Merck, Bayer등의 회사에서 계속 진행되어 왔다. 2000년 4월 Upjohn사에서는 지복스(Zyvox)라는 새로운 항생제 약물을 시판하게 되었고, 이것은 35년 만에 처음으로 선을 보인 새로운 유형의 항생제에 해당한다.

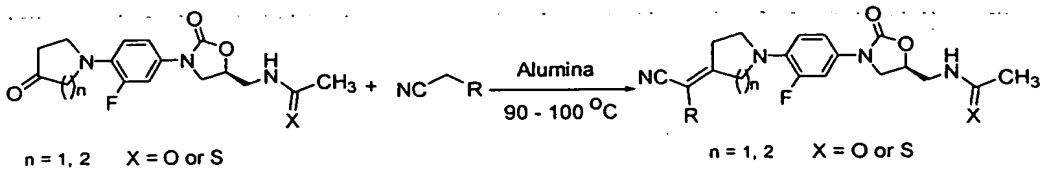
본 발명은 이와 같은 다제내성균주에 효능이 높은 항균제로서의 가능성이 있는 화합물과 그의 합성방법에 관한 것이다. 본 화합물의 항균 활성은 대조화합물로서 Upjohn사의 리네졸리드에 비해서 선택된 MRSA 및 그람양성균주에 대해서 2배 정도 우수한 항균 활성을 보이고 있다.

본 발명의 제조공정을 살펴보면, 일반식 (II)로 나타내어지는 옥사졸리디논 중간체(WO 9525106)에 여러가지 치환기가 치환된 화합물 (III), (IV)과의 반응에 의해 여러 가지의 메틸리덴 피페리딘 치환기를 도입한 일반식 (I)로 표시되는 옥사졸리디논 화합물을 제조하는 것이다.

[제조공정]

메틸리덴 피페리딘 유도체의 도입은 아래와 같은 두가지의 방법으로 완성할 수 있다. 방법 A은 Knoevenagel Condensation 반응을 이용했고, 방법 B에서는 Wadwards-Horner-Emmons 반응을 이용하였다. 각자의 제조공정을 살펴보면 다음과 같다.

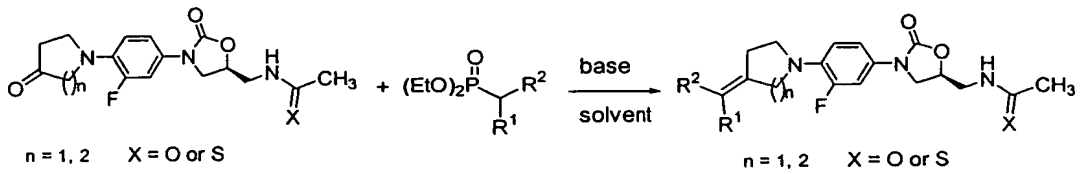
방법 A. Knoevenagel Condensation




(II) (III) (I)

상기 식 중 적당한 R 치환기로는 시아노기, 에톡시 카보닐기이다. X는 산소 또는 황 원자이다. 적당한 용매로는 디클로로메탄, 벤젠 혹은 무용매하에서 진행한다. 사용이 가능한 촉매로는 암모니아, 암모니아 염, 아민, 피페리딘, 포타슘 플루오리드, 세륨 플루오리드, 티타늄 클로리드, 알루미늄 옥사이드등이 가능하다. 반응 온도는 실온 또는 50-100 ℃가 적당하다.

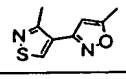
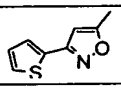
방법 B: Wadwards-Horner-Emmons 방법




(II) (IV) (I)

이 방법에서는 다양한 유도체의 도입이 가능하다. 우선 포스포네트를 활성화하는 과정이 필요하다. 활성화하기 위해서는 가장 적당한 염기로는 소듐 하이드리드, *n*-뷰틸리튬이 있다. 사용 가능한 용매로는 깨끗이 정제된 테트라히드로퓨란, 디 메톡시 에텐 등이 있다. 반응 온도는 0 ℃에서 실온사이가 적당하다. 그리고 피페리딘온을 첨가한 후 교반한다. 반응온도는 실온이며 또는 가열 환류도 가능하다. 모든 반응 과정은 질소 대기하에서 진행한다.

표 1. 합성된 옥사졸리디논 화합물

| 화합물 | R | R′ | 화합물 | R | R′ | 화합물 | R | R′ |
|---|---|---|---|---|---|---|---|---|
| 1[b] | CN | CN | 10 | H |  | 19 | H | $CH(NOCH_3)$ |
| 2[b] | CN | $CO_2Et$ | 11 | H | $CO_2Et$ | 20 | H | $C(NOH)CH_3$ |
| 3[b] | H | CN | 12 | H | $COCH_3$ | 21 | H | $C(NOCH_3)CH_3$ |
| 4[b] | H | $CO_2Et$ | 13 | $CH_3$ | $CO_2Et$ | 22 | H | $CH(OH)CH_3$ |
| 5[b] | H | $COCH_3$ | 14 | H | $CO_2Na$ | 23 | H | $CH(OAc)CH_3$ |
| 6 | CN | CN | 15 | Cl | $CO_2Et$ | 24 | H | $C(OCOCH_2Cl)_2CH_3$ |
| 7 | CN | $CO_2Et$ | 16 | CN | $CH_3$ | 25 | H | $C(OCOCHCl_2)_2CH_3$ |
| 8 | H | CN | 17 | H | CHO | 26 | CN | $CH_2CH_2NH_2$ |
| 9 | H |  | 18 | H | CH(NOH) | 27 | H | CN[a] |

[a], X = S; [b], n = 1.

다음의 화합물들은 본 발명에서 얻어진 일반식 (I)의 옥사졸리디논 화합물 중에서 대표적인 화합물들을 나타낸 것이다.

화합물 1. N-[(5S)-3-[3-플루오로-4-(3-디시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

화합물 2. N-[(5S)-3-[3-플루오로-4-(3-(1-시아노-1-에톡시카보닐)메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

화합물 3. N-[(5S)-3-[3-플루오로-4-(3-시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염.

화합물 4. N-[(5S)-3-[3-플루오로-4-(3-에톡시카보닐메틸리덴-피롤리딘-1-일)페

닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

화합물 5. N-[(5S)-3-[3-플루오로-4-(3-메틸카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

화합물 6. N-[(5S)-3-[3-플루오로-4-(4-디시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 7. N-[(5S)-3-[3-플루오로-4-(1-시아노-1-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 8. N-[(5S)-3-[3-플루오로-4-(4-시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 9. N-[(5S)-3-[3-플루오로-4-(4-(3-(2-티오펜닐)-5-이소옥사졸릴메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 10. N-[(5S)-3-[3-플루오로-4-(4-(3-(3-메틸-4-이소티아졸릴)-5-이소옥사졸릴)메틸리덴)피페리디닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 11. N-[(5S)-3-[3-플루오로-4-(4-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 12. N-[(5S)-3-[3-플루오로-4-(4-메틸카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 13. N-[(5S)-3-[3-플루오로-4-(4-(1-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 14. N-[(5S)-3-[3-플루오로-4-(4-카복시메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 나트륨 염

화합물 15. N-[(5S)-3-[3-플루오로-4-(4-(1-클로로-1-에톡시카보닐메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 16. N-[(5S)-3-[3-플루오로-4-(4-(1-시아노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 17. N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 18. N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염

화합물 19. N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 20. N-[(5S)-3-[3-플루오로-4-(4-(2-하이드록시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 21. N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 22. N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 23. N-[(5S)-3-[3-플루오로-4-(4-(2-아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 24. N-[(5S)-3-[3-플루오로-4-(4-(2-클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 25. N-[(5S)-3-[3-플루오로-4-(4-(2-디클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염

화합물 26. N-[(5S)-3-[3-플루오로-4-(4-(시아노메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염

화합물 27. N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-3-아미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염

실시예 1) N-[(5S)-3-[3-플루오로-4-(3-디시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-{3-[3-프르오로-4-(3-옥소-피롤리딘-1-일)-페닐]-2-옥소-옥사졸리딘-5-일메틸}-아세트아미드 (10 mg, 0.03 mmol)을 디클로로메탄 3 mL에 녹이고, $Al_2O_3$ (Basic, I, Aldrich, 30mg)과 malononitrile (4.3 mg, 0.07 mmol)과 molecular sieve (4A, 200 mg)를 넣고 0 ℃에서 3 시간 교반 하였다. 물을 가하여 씻어주고, 디클로로메탄으로 추출한 후 무수 황산마그네슘으로 건조하고 농축한 다음 관 크로마토그래피 (silica, EtOAc:MeOH=40:1)로 분리하여 목적 화합물 3.5 mg (31%)을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

1H NMR($CDCl_3$) : $\delta$ 7.48(d, $J$=14.7, 1H), 7.11(d, $J$=10.5, 1H), 6.78(t, $J$=3.0, 1H), 5.97(s, 1H), 4.78(m, 1H), 4.43(s, 2H), 4.03(t, J=9, 1H), 3.74(m, 3H), 3.61(m, 2H), 3.20(t, 2H), 2.00(s, 3H)

실시예 2) N-[(5S)-3-[3-플루오로-4-(3-(1-시아노-1-에톡시카보닐)메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

N-{3-[3-프르오로-4-(3-옥소-피롤리딘-1-일)-페닐]-2-옥소-옥사졸리딘-5-일메틸}-아세트아미드 (20 mg, 0.06 mmol)과 에틸 시아노아세테이트 (0.2 mL, excess), $Al_2O_3$ (Basic, I, Aldrich, 58 mg)을 디클로로메탄 2 mL에 녹이고 3 일간 교반 환류하였다. 물을 가하여 씻어주고, 디클로로메탄으로 추출한 후 무수 황산마그네슘으로 건조하고 농축한 다음 관 크로마토그래피 (silica, EtOAc:MeOH = 40:1)로 분리하여 생성물 15.0 mg (59%)을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

1H NMR($CDCl_3$, 300MHz) : $\delta$ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(M, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03(s, 3H), 1.37(t, J=7.14, 3H)

실시예 3) N-[(5S)-3-[3-플루오로-4-(3-시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염.

N-{3-[3-프르오로-4-(3-옥소-피롤리딘-1-일)-페닐]-2-옥소-옥사졸리딘-5-일메틸}-아세트아미드 (20 mg, 0.06 mmol)과 에틸 시아노아세테이트 (0.2 mL, excess), $Al_2O_3$ (Basic, I, Aldrich, 58 mg)을 디클로로메탄 2 mL에 녹이고 3 일간 교반

환류하였다. 물을 가하여 씻어주고, 디클로로메탄으로 추출한 후 무수 황산마그네슘으로 건조하고 농축한 다음 관 크로마토그래피 (silica, EtOAc:MeOH = 40:1)로 분리하여 생성물 15.0 mg (59%)을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

1H NMR($CDCl_3$, 300MHz) : $\delta$ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(M, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03(s, 3H), 1.37(t, J=7.14, 3H)

실시예 4) N-[(5S)-3-[3-플루오로-4-(3-에톡시카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

N-{3-[3-프르오로-4-(3-옥소-피롤리딘-1-일)-페닐]-2-옥소-옥사졸리딘-5-일메틸}-아세트아미드 (20 mg, 0.06 mmol)과 에틸 시아노아세테이트 (0.2 mL, excess), $Al_2O_3$ (Basic, I , Aldrich, 58 mg)을 디클로로메탄 2 mL에 녹이고 3 일간 교반 환류하였다. 물을 가하여 씻어주고, 디클로로메탄으로 추출한 후 무수 황산마그네슘으로 건조하고 농축한 다음 관 크로마토그래피 (silica, EtOAc:MeOH = 40:1)로 분리하여 생성물 15.0 mg (59%)을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

1H NMR($CDCl_3$, 300MHz) : $\delta$ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(M, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03(s, 3H), 1.37(t, J=7.14, 3H)

실시예 5) N-[(5S)-3-[3-플루오로-4-(3-메틸카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

N-{3-[3-프르오로-4-(3-옥소-피롤리딘-1-일)-페닐]-2-옥소-옥사졸리딘-5-일메틸}-아세트아미드 (20 mg, 0.06 mmol)과 에틸 시아노아세테이트 (0.2 mL, excess), $Al_2O_3$ (Basic, I , Aldrich, 58 mg)을 디클로로메탄 2 mL에 녹이고 3 일간 교반 환류하였다. 물을 가하여 씻어주고, 디클로로메탄으로 추출한 후 무수 황산마그네슘으로 건조하고 농축한 다음 관 크로마토그래피 (silica, EtOAc:MeOH = 40:1)로 분리하여 생성물 15.0 mg (59%)을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

1H NMR($CDCl_3$, 300MHz) : $\delta$ 7.45(d, J=15.12, 1H), 7.09(d, J=8.61, 1H), 6.80(m, 1H), 6.00(s, 1H), 4.77(M, 1H), 4.60(s, 2H), 4.31(m, 2H), 4.02(t, J=8.80, 1H), 3.75(m, 2H), 3.61(m, 3H), 3.18(m, 2H), 2.03(s, 3H), 1.37(t, J=7.14, 3H).

실시예 6) N-[(5S)-3-[3-플루오로-4-(4-디시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 20.0 mg (0.06 mmol)를 디클로로메탄 1 ml에 녹이고 말로노 나이트릴 3.8 mg (0.06 mmol)과 알루미늄 옥시드 17.2 mg (베이직 I, Aldrich)를 넣고 40 ℃에서 18 시간동안 교반한 후 반응혼합물을 물로 닦아주고 물층을 디클로로메탄으로 추출한다. 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 목적화합물 23.7 mg (99%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.47 (dd, J = 14.0 Hz, 1.2 Hz, 1H), 7.09 (dd, J = 8.7 Hz, 1.1 Hz, 1H), 6.92 (t, J = 9.1 Hz, 1H), 6.31 (s, br, 1H), 4.77 (m, 1H), 3.99 (t, J = 9.1 Hz, 1H), 3.76 (t, J = 7.1Hz, 1H), 3.67 (m, 2H), 3.26 (t, J = 5.5 Hz, 4H), 2.92 (t, J = 5.4 Hz, 4H), 1.99 (s, 3H). IR (KBr, $cm^{-1}$) 3300, 2924, 2232, 1750, 1656, 1518, 1418, 1382, 1216, 866, 752.

실시예 7) N-[(5S)-3-[3-플루오로-4-(1-시아노-1-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 2.42 g (6.93 mmol), 에틸 시아노아세테이트 6 mL와 알루미늄 옥시드 2.08 g (베이직 I, Aldrich, 20.4 mmol)를 90 - 100 ℃하에서 24시간동안 교반하였다. 반응혼합물을 셀라이트를 사용하여 여과한다. 여과액을 물로 닦아주고 디클로로메탄으로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼크로마토그래피로 분리하여 1.89 g (61%)의 목표 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz), ppm 7.42 (dd, J = 14.1 Hz, J = 2.6 Hz, 1H), 7.04 ( dd, J= 8.8 Hz, J = 2.1 Hz, 1H), 6.89 (t, J = 9.1 Hz, 1H), 6.68 (t, J = 5.3 Hz, 1H), 4.76 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.00 (t, J = 9.0 Hz, 1H), 3.74 ( m, 1), 3.62 (m, 2H), 3.30-3.22 (m, 4H), 3.16 (t, J = 5.5 Hz, 2H), 2.91 (t, J = 5.7 Hz, 2H), 2.00 ( s, 3H), 1.32 (t, J = 7.1 Hz; 3H).
IR (KBr, $cm^{-1}$) 924, 2232, 1750, 1656, 1518, 1418, 1382, 1216, 866, 752

실시예 8) N-[(5S)-3-[3-플루오로-4-(4-시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

소듐 히드리드 12.9 mg (80%, 0.43 mmol)를 정제한 테트라히드로퓨란 0.5 mL에 녹이고 디에틸 시아노메틸포스포네이트 55.7 mg (0.32 mmol)를 서서히 적가한 후 상온에서 1시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 100 mg (0.29 mmol)를 적가한 후 상온에서 3시간 동안 교반한 후 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼크로마토그래피로 분리하여 105 mg (64%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.47 (dd, J = 14.1 Hz, J = 2.55 Hz, 1H), 7.16 (dd, J = 8.79 Hz, J = 1.62 Hz, 1H), 6.94 (t, J = 2.49 Hz, 1H), 6.23 (t, J = 6.09 Hz, 1H), 5.12 (s, 1H) 4.78 (m, 1H), 4.16-4.00 (m 1H), 3.79- 3.72 (m, 1H), 3.69-3.58 (m, 2H), 3.20-3.10 (m, 4H), 2.78 (t, J = 5.28 Hz, 2H), 2.54 (t, J = 5.28 Hz, 2H), 2.00 (s, 3H).
$^{13}$C NMR (300MHz, $CDCl_3$) ppm 171.91(-$NHCOCH_3$), 164.45 (Ph, C-F), 157.01 (이소옥사졸 카르보닐), 155.09 (피페리디닐 C=), 114.65 (CN), 108.14 (H(CN)C=), 23.07 (-$NHCOCH_3$).
IR (KBr, $cm^{-1}$) 2232 (CN).
HRMS ($FAB^+$) $C_{19}H_{22}FN_4O_3$ Cacld. 373.1598, Found 373.1676.

실시예 9) N-[(5S)-3-[3-플루오로-4-(4-(3-(2-티오펜닐)-5-이소옥사졸릴메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

소듐 히드리드 17.2 mg (80%, , 0.57 mmol)를 정제한 테트라히드로퓨란 1.0 mL에 녹이고 디에틸 3-(2-티오펜일)-5-이소옥사졸메틸렌 포스포네이트 129 mg (0.43 mmol)를 천천히 적가한 후 반응혼합물을 상온에서 1시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 100 mg (0.29 mmol)를 적가한 후 상온에서 20시간동안 교반하였다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼크

로마토그래피로 분리하여 42.4 mg (20%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.43 (dd, J = 17.0, 13.5 Hz, 2H), 7.11 (t, J = 3.5 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.92 (t, J = 8.8 Hz, 1H), 6.32 (t, J = 7.2 Hz, 1H), 6.20 (s, 1H), 4.77 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.63 (m, 2H), 3.15 (m, 4H), 2.95 (t, J = 4.5 Hz, 2H), 2.52 (t, J = 4.5 Hz, 2H), 2.01 (s, 1H).

실시예 10) N-[(5S)-3-[3-플루오로-4-(4-(3-(3-메틸-4-이소티아졸릴)-5-이소옥사졸릴)메틸리덴)피페리디닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

80% 소듐 하이드리드 17.2 mg (0.57 mmol)를 깨끗하게 정제한 테트라히드로퓨란 1.0 mL에 녹이고 3-(2-이소티오펜일)-5-이소옥사졸메틸렌 포스포네이트 136 mg (0.43 mmol)를 천천히 적가한 후 반응혼합물을 상온에서 1시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 100 mg (0.29 mmol)를 적가하고 상온에서 20시간동안 교반한다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼크로마토그래피로 분리하여 31.9 mg (15%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 8.87 (s, 1H), 7.3 (dd, J = 18.0 Hz, J = 2.46 Hz, 1H), 7.07 (dd, J = 18 Hz, J = 1.8 Hz, 1H), 6.95 (s, 1H), 6.38 (t, J = 6.1 Hz, 1H), 6.32 (s, 1H), 6.23 (s, 1H), 4.77 (s, 1H), 4.07-3.98 (m, 1H), 3.79-3.71 (m, 1H), 3.69-3.52 (m, 2H), 3.18 (t, J = 5.34 Hz, 4H), 2.99 (t, J = 5.1 Hz, 2H), 2.60 (t, J = 5.1 Hz, 2H), 2.01 (s, 3H).

실시예 11) N-[(5S)-3-[3-플루오로-4-(4-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

소듐 하이드리드 3.1 mg (80%, 0.10 mmol)를 깨끗하게 정제한 디메톡시에탄 1 mL에 녹이고 트리에틸 포스포노아세테이트 2.1 mL (0.10 mmol)를 서서히 적가한 후 반응혼합물를 상온에서 2시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30.0 mg (0.09 mmol)를 적가한 후 상온에서 2시간동안 교반하였다. 반응혼합물에 물을 넣고 물층을 디클로로

메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 23.2 mg (64%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$), ppm 7.42 (dd, J = 12.0 Hz, J = 3.0 Hz, 1H), 7.05 (dd, J = 12.0 Hz, J = 3.0 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 6.47 (t, J = 4.5 Hz, 1H), 5.71 (s, 1H), 4.78 (m, 1H), 4.17 (q, J = 7.5 Hz, 2H), 3.78-3.60 (m, 5H), 3.11 (s, br, 4H), 2.49 (t, J = 3.0 Hz, 2H), 2.01 (s, 3H), 1.39 (t, J = 7.5 Hz, 3H).

실시예 12) N-[(5S)-3-[3-플루오로-4-(4-메틸카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

소듐 하이드리드 6.0 mg (80%, 0.20 mmol)를 정제한 디메톡시에탄 1 mL에 녹이고 디이에톡시 2-옥소프로필포스포네이트 38.5 uL (0.20 mmol)를 천천히 적가한 후 반응혼합물을 상온에서 2.5 시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 57.5 mg (0.17 mmol)를 적가한 후 상온에서 3시간 동안 교반하였다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 노란색의 목적 화합물 58.5 mg (91%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$), ppm 7.41 (dd, J = 14.2 Hz, 2.1 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 2.6 Hz, 1H), 6.92 (t, J = 9.1 Hz, 1H), 6.42 (t, J = 6.0 Hz, 1H), 6.09 (s, 1H), 4.76 (m, 1H), 4.00 (m, 1H). 3.74 (dd, J = 6.8 Hz, 2.4 Hz, 1H), 3.65 (m, 2H), 3.170-3.09 (m, overlap, 6H), 2.45 (t, *J* = 5.1 Hz, 2H), 2.20 (s, 3H), 2.01 (s, 3H).

실시예 13) N-[(5S)-3-[3-플루오로-4-(4-(1-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

소듐 하이드라이드 6.0 mg (80%, 0.20 mmol)를 깨끗하게 정제한 다이메톡시에테인 1 mL에 녹이고 트라이에틸 2-포스포노아세테이트 43 uL (0.20 mmol)를 천천히 적가한 후 반응혼합물을 상온에서 2시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 50.0 mg (0.14 mmol)를 적가한 후 상온에서 20 시간동안 교반하였다. 반응혼합물에 물을 넣고 물

층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하du 9.2 mg, (15%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$), ppm 7.43 (d, J = 14.1 Hz, 1H), 7.09-6.93 (m, 2H), 6.20 (t, J = 2.97 Hz, 1H), 4.77 (m, 1H), 4.21 (q, J = 14.3 Hz, 2H), 4.01 (t, J = 8.79 Hz, 1H), 3.79-3.60 (m, 3H), 3.10 (s, br, 4H), 2.81 (s, br, 2H), 2.54 (s, br, 2H), 2.01 (s, 3H), 1.91 (s, 3H), 1.31 (t, J = 14.3 Hz, 3H)

실시예 14) N-[(5S)-3-[3-플루오로-4-(4-카복시메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 나트륨 염의 제조

참고예 14-1) 알릴 디에톡시포스포닐 아세테이트

다이에틸 포스포노 아세트산 1.0 g (5.10 mmol)을 N,N-디메틸포름아마이드 5 mL에 녹이고 포타슘 카보네이트 1.06 g (7.65 mmol), 알릴 브로마이드 1.0 mL (11.7 mmol)를 적가하고 30-40 °C에서 1 시간동안 교반한 후 온도를 상온으로 내린 후 물을 넣고 에틸 아세테이트로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 50% 핵산-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 518 mg (43%)의 목적 화합물을 얻었다.

참고예 14-2) (5S)-N-[3-[플루오로-4-(4-알릴옥시카보닐메틸리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

소듐 하이드리드 15.5 mg (80%, 0.52 mmol)를 깨끗하게 정제한 다이메톡시에탄 1 mL에 녹이고 알릴 다이에톡시포스포닐 아세테이트 122 mg (0.52 mmol)를 천천히 적가한 후 상온에서 2시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 50.0 mg (0.14 mmol)를 적가한 후 상온에서 20시간동안 교반한후 3.5 시간동안 가열 환류하였다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 노란색의 목적 화합물 110 mg (59%)를 얻었다.

실시예 14-3) N-[(5S)-3-[3-플루오로-4-(4-카르복실메틸리덴피페리덴)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 나트륨 염의 제조

(5S)-N-[3-[플루오로-4-(4-알릴옥시카보닐메틸리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 98 mg (0.23 mmol), 소듐 2-에틸 헥사노에트 55.8 mg (0.34 mmol), 트리페닐 포스핀 6.0 mg (0.02 mmol)과 테트라키스 트라이페닐 포스핀 팔라듐 (0) 5.2 mg (0.005 mmol)를 디클로로메탄 1 mL에 넣고, 상온에서 20시간동안 교반한 후 아세톤을 넣고 생성된 고체를 여과하고 에테로 닦아주고 흰색의 목적 화합물 55.8 mg (59%)를 얻었다.

$^1$H NMR (300 MHz, $CD_3OD$), ppm 7.47 (dd, J = 14.5 MHz, J = 1.86 MHz, 1H), 7.12 (dd, J = 8.79 MHz, J = 1.14 MHz, 1H), 7.03 (t, J = 9.09 MHz, 1H), 5.73 (s, 1H), 4.76 (m, 1H), 4.10 (t, J = 9.06 MHz, 1H), 3.77 (dd, J = 9.06 MHz, J = 6.57 MHz, 1H), 3.54 (d, J = 4.95 MHz, 2H), 3.06 (m, 4H), 2.95 (d, J = 4.74 MHz, 2H), 2.38 (t, J = 12.2 MHz, 2H), 1.95 (s, 3H).

실시예 15) N-[(5S)-3-[3-플루오로-4-(4-(1-클로로-1-에톡시카보닐메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

소듐 하이드리드 7.2 mg (80%, 0.24 mmol)를 정제한 테트라히드로퓨란 1 mL에 녹이고 트라이에틸 2-클로로-2-포스포노아세테이트 51.4 uL (0.24 mmol)를 천천히 적가한 후 상온에서 1.5시간정도 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 60.0 mg (0.17 mmol)를 적가한 후 상온에서 4 시간동안 교반하였다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 30 mg (38%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.41 (dd, J = 14.2 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 1.8 Hz, 1H), 6.91 (t, J = 9.2 Hz, 1H), 6.57 (t, J = 6.0 Hz, 1H), 4.76 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.98 (t, J = 6.2 Hz, 1H), 3.74 (t, J = 8.8 Hz, 1H), 3.62 (m, 2H), 3.12 (m, 4H), 2.98 (t, J = 5.5 Hz, 2H), 2.79 (t, J = 5.5 Hz, 2H), 1.98 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

실시예 16) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

소듐 하이드리드 7.4 mg (80%, 0.246 mmol)를 깨끗하게 정제한 테트라히드로퓨란

1 mL에 녹이고 다이에틸 2-사이아노메틸포스포노아세테이트 37 uL (0.21 mmol)를 천천히 적가한 후 상온에서 1.5 시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 60.0 mg (0.17 mmol)를 적가한 후 상온에서 20시간동안 교반하고 60℃에서 20시간동안 교반한다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 21 mg (32%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.43 (dd, J = 14.2 Hz, 2.6 Hz, 1H), 7.05 (dd, J = 8.8 Hz, 1.7 Hz, 1H), 6.91 (t, J = 9.1 Hz, 1H), 6.40 (t, J = 6.3 Hz, 1H), 4.77 (m, 1H), 4.00 (m, 1H), 3.76 (m, 1H), 3.64 (m, 2H), 3.12 (m, 4H), 2.77 (t, J = 5.4 Hz, 2H), 2.54 (t, J = 5.5 Hz, 2H), 2.00 (s, 3H), 1.93 (s, 3H).

실시예 17) N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

참고예 17-1) N-(5S)-[3-[3-플루오로-4-(4-알릴-4-하이드록시피페리디닐)페닐]-2-옥소-5-옥사졸리디닐]메틸아세트아미드

N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 100 mg (0.29 mmol)를 테트라히드로퓨란/물 3 mL (v/v, 1/3)에 녹인고 인듐 39.4 mg (0.34 mmol)과 알릴 브로미드 37 uL (0.43 mmol)를 넣고 3 시간동안 교반한다. 반응혼합물을 여과하고 여과액을 메틸렌 클로리드로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 흰색 목적 화합물 96.5 mg (86%)를 얻었다.

참고예 17-2) N-[(5S)-3-[3-플루오로-4-(2,3,4-트리하이드록시프로필리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

N-(5S)-[3-[3-플루오로-4-(4-알릴-4-하이드록시피페리디닐)페닐]-2-옥소-5-옥사졸리디닐]메틸아세트아미드 20 mg (0.05 mmol), N-메틸모폴린 N-옥시드 (50% 수용액, 19.2 mmol), 촉매양의 오스뮴 테트라옥시드를 80% 아세톤에 넣고 상온에서 1시간동안 교반하였다. 마그네슘 설페이트를 넣고 10 분동안 교반하고 고체를 여과하여 여과액을 감압 농축시킨후 노란색 고체 15.4 mg (68%)를 얻었다.

참고예 17-3) N-[(5S)-3-[3-플루오로-4-(1-히드록시-2-포르밀프로필)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

N-[(5S)-3-[3-플루오로-4-(1-히드록시-2,3-다이하이드록시프로필리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 1.38 g (3.20 mmol)를 50% 메탄올 수용액에 녹인후 소듐 퍼아이오데이트 883 mg (4.13 mmol)를 가하고 상온에서 1.5 시간동안 교반한 후 에틸 아세테이트로 몇 번 추출한다. 유기층을 마그네슘 설페이트로 건조한고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 612 mg (49%)의 목적 화합물을 얻었다.

실시예 17-4) N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

N-[(5S)-3-[3-플루오로-4-(4-하이드록시-4-(2-포르밀)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 570 mg (1.45 mmol)를 디클로로메탄 10 mL에 녹이고 트라이에틸아민 505 uL (3.63 mmol)과 4-N,N-디메틸아미노피리딘 354 mg (2.90 mmol)를 가하고 10분동안 교반한 후 메탄설폰일 클로라이드 224 uL (2.90 mmol)를 천천히 가하고 0 ℃에서 3 시간동안 교반한다. 혼합물을 물로 닦아주고 물층을 다시 메틸렌 클로리드로 추출한다. 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 120 mg (22%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz) ppm 10.0 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 14.1 Hz, 2.4 Hz, 1H), 7.07 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 6.95 (t, J = 9.1 Hz, 1H), 6.19 (t, J = 5.9 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 4.76 (m, 1H), 4.02 (t, J = 8.9 Hz, 1H), 3.76 (t, J = 6.7 Hz, 1H), 3.61 (m, 2H), 3.20 (m, 4H), 3.01 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.5 Hz, 2H), 2.02 (s, 3H).

실시예 18) N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 에탄올/물 1 mL (v/v, 1/2)에 녹이고 소듐 카보네이트 5.1 mg (0.05 mmol)과 하이드록시아민 염산 염 7.2 mg (0.10

mmol)를 넣고 50 °C에서 2 시간동안 교반한 후 물을 넣고 물층을 에틸 아세테이트로 추출한다. 유기층을 마그네슘 설페이트로 건조한고 여과하여 감압 농축시킨 후 목적화합물 22 mg (71%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CD_3OD$) ?ppm 8.06 (d, J = 10.4 Hz, 1H), 7.46 (dd, J = 14.5 Hz, 2.5 Hz, 1H), 7.13 (dd, J = 8.8 Hz, 2.3 Hz, 1H), 7.02 (t, J = 9.1 Hz, 1H), 5.94 (d, J = 10.4 Hz, 1H), 4.77 (m, 1H), 4.09 (t, J = 9.1Hz, 1H), 3.76 (m, 1H), 3.52 (d, J = 7.3 Hz, 2H), 3.08 (m, 4H), 2.65 (t, J = 5.4 Hz, 1H), 2.59 (t, J = 5.5 Hz, 1H), 2.47 (m, 2H), 1.95 (s, 3H).

실시예 19) N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸이덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 에탄올/물 1 mL (v/v, 1/2)에 녹이고 소듐 카보네이트 5.1 mg (0.05 mmol)과 메톡시아민 염산염 8.7 mg (0.10 mmol)를 넣고 50 °C에서 2 시간동안 교반한 후 물을 넣고 물층을 에틸 아세테이트로 추출한다. 유기층을 마그네슘 설페이트로 건조한고 여과하여 감압 농축시킨 후 목적화합물 25.7 mg (80%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CD_3OD$) ?ppm 8.08 (d, J = 10.4 Hz, 1H), 7.46 (dd, J = 14.3 Hz, 2.3 Hz, 1H), 7.13 (dd, J = 8.9 Hz, 2.4 Hz, 1H), 7.02 (t, J = 9.2 Hz, 1H), 5.90 (d, J = 10.4 Hz, 1H), 4.77 (m, 1H), 4.079 (t, J = 9.1 Hz, 1H), 3.80-3.74 (m, 4H), 3.55 (d, J = 4.7 Hz, 2H), 3.09 (m, 4H), 2.65 (t, J = 5.3 Hz, 1H), 2.59 (t, J = 5.2 Hz, 1H), 2.47 (t, J = 5.0 Hz, 2H), 2.00 (s, 3H).

실시예 20) N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-(3-플루오로-4-(4-아세틸에틸리덴피페리디닐))-2-옥소-5-옥사졸리딘일]메틸아세트아미드 40 mg (0.10 mmol)를 에탄올/물 1 mL (v/v, 1/2)에 녹이고 소듐 카보네이트 6.6 mg (0.06 mmol)과 하이드록시 아민 염산 염 9.30 mg (0.13 mmol)를 넣고 50 °C에서 2 시간동안 교반한 후 물을 넣고 물층을 에틸 아세테이트로 추출한다. 유기층을 마그네슘 설페이트로 건조한고 여과하여 감압 농축시킨 후 목적화합물 17.8 mg (43%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사

용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ?ppm 7.44 (dd, J = 14.6 Hz, 1.1 Hz, 1H), 7.11 (dd, J = 8.9 Hz, 1.7 Hz, 1H), 7.04 (m, 1H), 5.70 (s, 1H), 4.75 (m, 1H), 4.08 (t, J = 8.9 Hz, 1H), 3.75 (dd, J = 9.1Hz, 6.5 Hz, 1H), 3.52 (m, 2H), 3.18 (t, J = 5.5 Hz, 1H), 3.08 (t, J = 11.8 Hz, 2H), 2.99 (t, J = 5.7 Hz, 2H), 2.69 (t, J = 5.5 Hz, 1H), 2.42 (m, 2H), 1.96 (s, 3H).

실시예 21) N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-(3-플루오로-4-(4-아세틸에틸리덴피페리디닐))-2-옥소-5-옥사졸리딘일]메틸아세트아미드 40 mg (0.10 mmol)를 메탄올/디클로로메탄 2 mL (v/v, 1/1)에 녹이고 포타슘 카보네이트 14.2 mg (0.10 mmol)과 메톡시아민 염산 염 12.9 mg (0.16 mmol)를 넣고 50 °C에서 2시간동안 교반한 후 물을 넣고 물층을 에틸 아세테이트로 추출한다. 유기층을 마스네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 목적화합물 32.1 mg (74%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.45 (dd, J = 14.5 Hz, 2.3 Hz, 1H), 7.23 (dd, J = 5.5 Hz, 2.3 Hz, 1H), 7.04 (m, 1H), 5.65 (s, br, 1H), 4.75 (m, 1H), 4.08 (t, J = 9.0 Hz, 1H), 3.76 (m, 4H), 3.55 (d, J = 5.0 Hz, 2H), 3.18 (t, J = 4.5 Hz, 1H), 3.04 (m, 4H), 2.74 (t, J = 4.5 Hz, 1H), 2.42 (t, J = 3.0 Hz, 2H), 1.91 (s, 3H).

실시예 22) N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

N-[(5S)-3-(3-플루오로-4-(4-아세틸에틸리덴피페리디닐))-2-옥소-5-옥사졸리딘일]메틸아세트아미드 25 mg (0.06 mmol)를 디클로로메탄/메탄올 2 mL (v/v, 1/1)에 녹이고 소듐 보로히드리드 4.8 mg (0.13 mmol)를 가한다. 반응 혼합물을 상온에서 4 시간동안 교반한 후 포화 암모늄 클로라이드수용액을 넣고 교반한 후 메틸렌 클로리드로 추출한다. 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 흰색고체 19.4 mg (77%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.39 (dd, J = 14.2 Hz, 2.5 Hz, 1H), 7.03 (dd, J

= 8.8 Hz, 2.3 Hz, 1H), 6.90 (t, J = 9.1 Hz, 1H), 6.50 (s, br, 1H), 5.28 (d, J = 8.5 Hz, 1H), 4.75 (m, 1H), 4.63 (m, 1H), 3.99 (t, J = 9.1 Hz, 1H), 3.75 (m, 1H), 3.63 (m, 2H), 3.02 (m, 4H), 2.47 (m, 2H), 2.34 (m, 2H), 2.00 (s, 3H), 1.29 (d, J = 11.3 Hz, 3H).

실시예 23) N-[(5S)-3-[3-플루오로-4-(4-(2-아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 디클로로메탄 1 mL에 녹이고 피리딘 11 uL (0.130 mmol)과 정제한 아세틸 클로라이드 9.2 uL (0.13 mmol)를 천천히 가하고 0 ℃를 유지하면서 30 분동안 교반한다. 반응혼합물을 물로 닦아주고 물층을 디클로로메탄으로 추출하고 유기층은 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 노란색의 목적화합물 18.8 mg (57%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz), ppm 7.39 (dd, J = 14.0 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.6 Hz, 2.3 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H), 6.41 (t, J = 6.1 Hz, 1H), 5.62 (m, 1H), 5.22 (d, J = 8.9 Hz, 1H), 4.75 (m, 1H), 4.00 (t, J = 9.1 Hz, 1H), 3.73 (m, 1H), 3.63 (m, 2H), 3.04 (m, 4H), 2.54 (m, 1H), 2.45 (m, 1H), 2.34 (m, 2H), 2.03-2.01 (2s, 6H), 1.28 (d, J = 6.4 Hz, 3H).

실시예 24) N-[(5S)-3-[3-플루오로-4-(4-(2-클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 디클로로메탄 1 mL에 녹이고 피리딘 11 uL (0.13 mmol), 정제한 클로로아세틸 클로리드 10 ?L (0.13 mmol)를 천천히 가하고 0 ℃를 유지하면서 30 분동안 교반한다. 반응혼합물을 물로 닦아주고 물층을 메틸렌 클로리드로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 노란색의 목적화합물 25.1 mg (70%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz), ppm 7.39 (dd, J = 14.3 Hz, 2.4 Hz, 1H), 7.02 (dd, J = 8.9 Hz, 2.3 Hz, 1H), 6.89 (t, J = 9.0 Hz, 1H), 5.70 (m, 1H). 5.21 (d, J = 9.1 Hz,

1H), 7.45 (m, 1H), 4.02-3.96 (m, 3H), 3.74 (t, J = 9.0 Hz, 1H), 3.62 (m, 2H), 3.10-3.06 (m, 2H), 3.06-2.99 (m, 2H), 2.57 (m, 1H), 2.43 (m, 1H), 2.35 (m, 2H), 2.01 (s, 3H), 1.33 (d, J = 6.3 Hz, 3H).

실시예 25) N-[(5S)-3-[3-플루오로-4-(4-(2-디클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(2-하이드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 디클로로메탄 1 mL에 녹이고 피린딘 11 uL (0.13 mmol), 정제한 다이클로로 아세틸클로라이드 13 uL (0.13 mmol)를 천천히 가하고 0 °C를 유지하면서 30 분동안 교반한다. 반응혼합물을 물로 닦아주고 물층을 디클로로메탄으로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 노란색의 목적 화합물 26.4 mg (69%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz), ppm 7.40 (dd, J = 14.1 Hz, 2.5 Hz, 1H), 7.02 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.54 (t, J = 5.9 Hz, 1H), 5.90 (s, 1H), 5.72 (m, 1H), 5.26 (d, J = 8.9 Hz, 1H), 4.76 (m, 1H), 4.00 (t, J = 9.1 Hz, 1H), 3.74 (m, 1H), 3.62 (m, 2H), 3.11 (m, 2H), 2.97 (m, 2H), 2.56 (m, 1H), 2.49-2.32 (m, 3H), 2.02 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H).

실시예 26) N-[(5S)-3-[3-플루오로-4-(4-(시아노메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 30 mg (0.08 mmol)를 1,4-다이옥산 2 mL에 녹이고 Lawesson's reagent 35 mg (0.08 mmol)을 가하고 100 °C에서 18 시간동안 교반한다. 반응혼합물을 물로 닦아주고 다시 디클로로메탄으로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 18.3 mg (52%)의 목적 화합물을 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR ($CDCl_3$, 300 MHz), ppm 8.39 (s, br, 1H), 7.45 (d, J = 13.5 Hz, 1H), 7.05 (s, br, 2H), 5.21 (s, 1H), 4.99 (m, 1H), 4.21-4.18 (m, 1H), 4.13-4.04 (m, 2H),

3.84 (t, J = 9.2 Hz, 1H), 3.23-3.16 (m, 4H), 2.81 (t, J = 5.4 Hz, 2H), 2.59 (s, 5H).

실시예 27) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-3-아미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산염의 제조

참고예 27-1) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-2-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

소듐 하이드리드 7.4 mg (60%, 0.25 mmol)를 정제한 테트라히드로퓨란 6 mL에 녹이고 트리이에틸 3-사이아노-3-(다이에톡시포스포릴)-프로피오니산 에틸이스터 테트라히드로퓨란 0.5 mL에 녹여서 천천히 가한 후 상온에서 2.5시간동안 교반하고 N-[(5S)-3-[3-플루오로-4-(4-옥소피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 300 mg (0.86 mmol)를 적가한후 상온에서 20 시간동안 교반한다. 반응혼합물에 물을 넣고 물층을 디클로로메탄으로 추출하여 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨후 10% 메탄올-에틸 아세테이트를 사용하여 컬럼 크로마토그래피로 분리하여 고체의 목적 화합물 84.8 mg (22%)를 얻었다.

$^1$H NMR (300 MHz, $CDCl_3$) ppm 7.43 (dd, J = 14.2 Hz, 2.6 Hz, 1H), 7.05 (dd, J = 8.8 Hz, 1.7 Hz, 1H), 6.91 (t, J = 9.1 Hz, 1H), 6.40 (t, J = 6.3 Hz, 1H), 4.77 (m, 1H), 4.00 (m, 1H), 3.76 (m, 1H), 3.64 (m, 2H), 3.12 (m, 4H), 2.77 (t, J = 5.4 Hz, 2H), 2.54 (t, J = 5.5 Hz, 2H), 2.00 (s, 3H), 1.93 (s, 3H).

참고예 27-2) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-4-히드록시뷰틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

N-[(5S)-3-[3-플루오로-4-(4-(1-사이아노-2-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 48 mg (0.11 mmol)를 테트라히드로퓨란/물 3 mL (1/2)에 녹이고 소듐 보로히드리드 10 mg (0.27 mmol)를 가한 후 0 ℃에서 3 시간동안 교반하고 상온에서 16 시간동안 교반한다. 포화 암모늄 클로라이드수용액을 가하고 5 분동안 교반한 후 물층을 에틸 아세테이트로 추출하고 유기층을 마그내슘 설페이트로 건조하고 여과하여 감합 농축시킨 후 노란색 고체 38.9 mg (89%)를 얻었다.

참고예 27-3) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-4-메탄설폰일옥시)뷰틸이덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-4-하이드록시뷰탈리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 38.9 mg (0.09 mmol), 트라이에틸아민 48 uL (0.35 mmol)을 디클로로메탄 1 mL에 녹이고 0 °C하에서 메탄설폰일 클로라이드 21 uL (0.27 mmol)를 천천히 가한 후 2 시간동안 교반한다. 반응 혼합물을 물로 닦아주고 물층을 메틸렌 클로리드로 추출한 후 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 목적화합물 46 mg (99%)를 얻었다.

참고예27-4) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-4-아지도)뷰틸리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드

N-[(5S)-3-[3-플루오로-4-(4-(1-사이아노-4-메탄설폰일옥시)뷰틸이덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 46 mg (0.09 mmol)를 N,N-다이메틸 포름아미이드 1 mL에 녹이고 소듐 아자드 48 mg (0.74 mmol)를 넣고 80 °C에서 18 시간동안 교반한다. 반응혼합물에 물을 넣고 물층을 에틸 아세테이드로 추출한다. 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 목적 화합물 33.3 mg (81%)를 얻었다.

실시예 27-5) N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-3-아미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염의 제조

N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-4-아지도)뷰틸리덴)피페리디닐]페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 33.3 mg (0.08 mmol)를 테트라히드로퓨란/물 1 mL (1/3)에 녹이고 인듐 35 mg (0.30 mmol), 6N 염산 290 uL을 가하고 상온에서 10 시간동안 교반한다. 반응 혼합물을 감압 여과 하고 여과액을 에틸 아세테이트로 몇 번 닦아주고 물층을 3N 수산화 나트륨으로 중화한다. 물층을 에틸 아세테이트로 추출하고 유기층을 마그네슘 설페이트로 건조하고 여과하여 감압 농축시킨 후 목적화합물 13.0 mg (41%)를 얻었다. 얻어진 화합물을 에틸 에테르에 포화된 염산을 사용하여 염산 염을 합성하였다.

$^1$H NMR (300 MHz, $CDCl_3$), ppm 7.41 (dd, J = 14.0, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.89 (t, J = 9.2Hz, 1H), 6.73 (s, br, 1H), 4.74 (m, 1H), 4.98 (t, J = 8.9 Hz, 1H), 3.75 (t, J = 9.2Hz, 1H), 3.62 (t, J = 5.5 Hz, 2H), 3.49 (t, J = 6.6 Hz, 2H), 3.11 (m, 4H), 2.79 (t, J = 5.9Hz, 2H), 2.63-2.51 (m, 4H), 1.96 (s, 3H).

**생체외 항균활성 시험** : 본 발명에서 합성된 대표적인 화합물들의 생체외 항균력은 뮐러 힌튼 아가(Mueller Hinton Agar)를 사용한 한천희석(Agar Dilution)방법에 의해 37 ℃에서 18시간 배양한 후 그 2배씩 단계적으로 희석하여 접종한 평판을 일렬로 나열하고 육안으로 관찰하여 표기화합물의 최소발육 억제농도 (MIC, $\mu$g/mL)를 정하였다. 그 시험결과를 다음의 표2에 요약하였다.

표2) 화합물의 항균활성 시험 결과 (MIC, $\mu$g/mL)

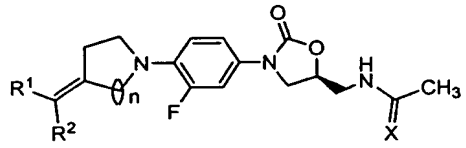
| Microorganism | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. aureus ATCC 29213 | 2 | 4 | 2 | 32 | 16 | 16 | 8 | 16 | 8 | 32 | 2 | 8 |
| MRSA C2207 | 4 | 4 | 2 | 32 | 16 | 8 | 8 | 16 | 8 | 16 | 2 | 4 |
| MRSA C5100 | 4 | 4 | 2 | 16 | 8 | 8 | 8 | 8 | 4 | 16 | 2 | 4 |
| MRSA C6068 | 2 | 4 | 1 | 16 | 8 | 8 | 16 | 8 | 4 | 16 | 2 | 4 |
| CRSA C6043 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 8 | 8 | 16 | 2 | 4 |
| CRSA C1062 | 4 | 4 | 2 | 32 | 16 | 8 | 8 | 16 | 16 | 16 | 2 | 8 |
| MSSA C7142 | 4 | 4 | 2 | 32 | 8 | 16 | 16 | 8 | 8 | 8 | 2 | 4 |
| MSSA C2214 | 4 | 4 | 4 | 16 | 16 | 16 | 16 | 16 | 8 | 8 | 2 | 8 |
| S. epidermidis ATCC12228 | 1 | 1 | 0.5 | 4 | 2 | 2 | 1 | 4 | 1 | 2 | 0.5 | 1 |
| S. epidermidis C2230 | 2 | 2 | 2 | 8 | 4 | 8 | 8 | 16 | 4 | 4 | 2 | 2 |
| S. epidermidis C2235 | 2 | 2 | 1 | 8 | 4 | 4 | 8 | 8 | 1 | 4 | 2 | 2 |
| E. faecalis ATCC29212 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 16 | 8 | 8 | 2 | 16 |
| E. faecalis C6288 | 4 | 4 | 2 | 16 | 16 | 8 | 16 | 16 | 4 | 8 | 2 | 4 |
| E. faecalis C6291 | 4 | 4 | 2 | 16 | 8 | 8 | 16 | 8 | 8 | 4 | 2 | 8 |
| E. faecium C2252 | 4 | 4 | 2 | 16 | 8 | 8 | 8 | 8 | 8 | 4 | 2 | 8 |
| E. faecium C6301 | 2 | 2 | 2 | 16 | 8 | 8 | 8 | 8 | 4 | 2 | 2 | 4 |
| S. pyogenes ATCC8668 | 1 | 1 | 0.5 | 2 | 2 | 2 | 8 | 8 | 4 | 2 | 2 | 2 |
| S. pyogenes C6003 | 4 | 4 | 2 | 16 | 8 | 8 | 0.2(5) | 4 | 2 | 2 | 0.5 | 8 |
| S. pyogenes C6012 | 1 | 1 | 0.5 | 4 | 2 | 2 | 16 | 16 | 8 | 8 | 2 | 1 |
| VRE C6487 | 4 | 2 | 4 | 16 | 4 | 8 | 2 | 1 | 1 | 2 | 0.5 | 8 |
| VRE C6488 | 2 | 2 | 4 | 16 | 8 | 8 | 8 | 8 | 8 | 4 | 1 | 8 |

표3) 화합물의 항균활성 시험 결과 (MIC, ug/mL)

| Microorganism | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | LZD | VAN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S. aureus ATCC 29213 | 8 | 8 | 8 | 16 | 8 | 16 | 16 | 16 | 2 | 2 | 4 | 1 |
| MRSA C2207 | 8 | 4 | 8 | 16 | 16 | 8 | 16 | 16 | 2 | 2 | 4 | 1 |
| MRSA C5100 | 4 | 4 | 8 | 8 | 8 | 16 | 16 | 8 | 1 | 1 | 2 | 2 |
| MRSA C6068 | 4 | 4 | 4 | 8 | 4 | 8 | 8 | 8 | 2 | 2 | 2 | 1 |
| CRSA C6043 | 8 | 4 | 8 | 16 | 8 | 16 | 16 | 16 | 2 | 2 | 2 | 2 |
| CRSA C1062 | 8 | 4 | 8 | 32 | 16 | 16 | 8 | 16 | 2 | 2 | 4 | 2 |
| MSSA C7142 | 8 | 4 | 16 | 16 | 16 | 16 | 16 | 16 | 2 | 2 | 4 | 2 |
| MSSA C2214 | 8 | 8 | 8 | 16 | 16 | 16 | 16 | 16 | 2 | 2 | 4 | 1 |
| S. epidermidis ATCC12228 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 0.5 | 0.5 | 0.5 | 1 |
| S. epidermidis C2230 | 4 | 4 | 4 | 16 | 4 | 8 | 8 | 8 | 1 | 1 | 2 | 2 |
| S. epidermidis C2235 | 4 | 2 | 4 | 8 | 4 | 8 | 8 | 8 | 0.5 | 0.5 | 2 | 2 |
| E. faecalis ATCC29212 | 8 | 4 | 8 | 16 | 8 | 8 | 8 | 8 | 2 | 2 | 4 | 4 |
| E. faecalis C6288 | 4 | 2 | 4 | 8 | 4 | 8 | 16 | 8 | 1 | 1 | 2 | 2 |
| E. faecalis C6291 | 4 | 4 | 4 | 8 | 8 | 8 | 16 | 8 | 1 | 1 | 2 | 2 |
| E. faecium C2252 | 4 | 4 | 4 | 8 | 4 | 8 | 16 | 8 | 1 | 1 | 2 | 1 |
| E. faecium C6301 | 4 | 4 | 4 | 8 | 4 | 8 | 8 | 8 | 1 | 1 | 2 | 1 |
| S. pyogenes ATCC8668 | 2 | 1 | 1 | 2 | 2 | 0.5 | 2 | 2 | 0.5 | 0.5 | 0.5 | 0.12 |
| S. pyogenes C6003 | 4 | 2 | 4 | 8 | 8 | 8 | 8 | 8 | 0.25 | 0.25 | 2 | 4 |
| S. pyogenes C6012 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 0.25 | 0.25 | 0.5 | 0.5 |
| VRE C6487 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 0.5 | 0.5 | 2 | >32 |
| VRE C6488 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 0.5 | 0.5 | 2 | >32 |

특허청구범위

[제 1항] 다음 일반식 (I)로 표시되는 알케닐 피페리디닐 옥사졸리디논 유도체 및 약제학적으로 허용되는 염

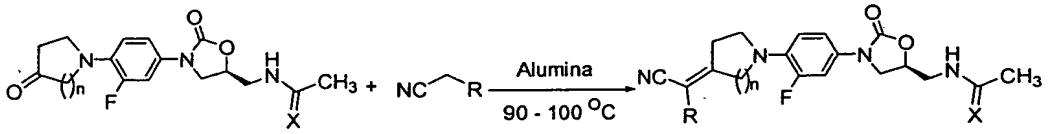



n = 1, 2

(I)

상기 식 중 X는 산소 황 원자를 나타내고, n은 1 또는 2를 표시하며, $R^1$과 $R^2$는 수소, 시아노기, 알킬 할로겐, 아세톡시, 에틸카르보닐, 알코올, 아민, 헤테로고리 치환체를 나타낸다. 알킬 치환체로는 메틸, 에틸, 프로필기를 말하고, 할로겐으로는 브로모, 클로로기를 말한다. 아세톡시는 모노클로린, 디클로린으로 치환된 구조를 말한다. 옥심은 하이드록시옥심과 메톡시옥심을 말한다. 헤테로고리 치환체는 불포화된 5환 헤테로고리를 말하며, 헤테로고리에는 산소, 질소, 황원자를 적어도 한 개 이상 포함하고 있는 구조를 말한다. 이러한 예로는 이소옥사졸, 티오펜, 이소티아졸, 티아졸, 티아디아졸등을 말한다.

[제 2 항] 일반식 (II)의 화합물과 일반식 (III)의 화합물을 반응시켜 얻는것이 특징인 일반식 (I) 화합물의 제조 방법




n = 1, 2 X = O or S

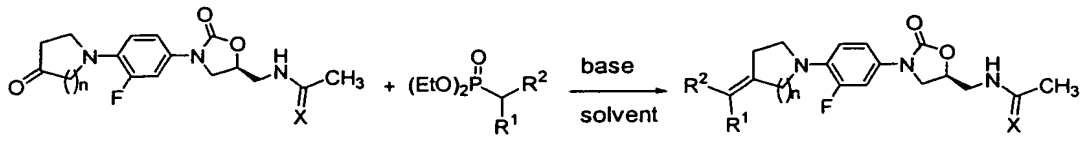
n = 1, 2 X = O or S

(II) (III) (I)

상기에서는 일반식 (III)으로 표시된 화합물은 말로노니트릴과 에틸 시아노기, 아세테이트기가 적당하다. 여기서 이용되는 Knoevenagel Condensation방법은 메틸렌 클로리드, 벤젠등 용매 혹은 무용매하에서 진행되며, 촉매로는 알루미늄 옥사이드, 아민등 가능하며, 반응 온도는 90-100 °C 가 정당하다.

상기식에서 n, R, $R^1$, $R^2$는 각각 제1항에서 정의한 것과 동일하다.

[제 3 항] ] 일반식 (II)의 화합물과 일반식 (III)의 화합물을 반응시켜 얻는것이 특징인 일반식 (I) 화합물의 제조 방법




n = 1, 2 X = O or S

(II)



(IV)

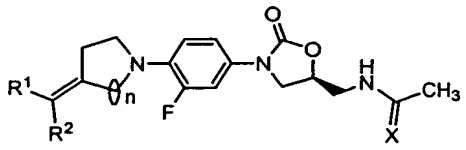


n = 1, 2 X = O or S

(I)

상기에서는 일반식 (IV)로 포시되는 다양한 유도체가능하며, 우선 화합물 (IV)를 활성화해야만 한다. 즉 용매는 테트라히드로퓨란, 디메틸에탄, 디메틸포름아미드등을 사용하며, 염기로서는 소듐 히드리드, 삼차-부톡사이드 포타슘 염를 사용하여 포스포네이트를 활성화한 후 화합물 (II)를 넣어서 Wadwards-Horner-Emmons 반응을 실행한다. 이때 반응 온도는 40 ~ 100 °C가 가능하나 25 °C가 적당하다.
상기식에서 n, R, $R^1$, $R^2$ 는 각각 제1항에서 정의한 것과 동일하다.

[제 4 항] 청구1항에서 다음의 화학식을 가지는 화합물



n = 1, 2

상기식에서 n, X, R, $R^1$, $R^2$ 는 각각 제1항에서 정의한 것과 동일하다.

[제 5 항] 청구 4항에서 n이 1인 화합물

[제 6 항] 청구 5항에서 n이 1인 화합물은 다음과 같다.
N-[(5S)-3-[3-플루오로-4-(3-디시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(3-(1-시아노-1-에톡시카보닐)메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;

N-[(5S)-3-[3-플루오로-4-(3-시아노메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염;
N-[(5S)-3-[3-플루오로-4-(3-에톡시카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(3-메틸카보닐메틸리덴-피롤리딘-1-일)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염.

[제 7 항] 청구 4항에서 n이 2인 화합물

[제 8 항] 청구 7항에서 n이 2인 화합물은 다음과 같다.
N-[(5S)-3-[3-플루오로-4-(4-디시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(1-시아노-1-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-시아노메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산염;
N-[(5S)-3-[3-플루오로-4-(4-(3-(2-티오펜닐)-5-이소옥사졸릴메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(3-(3-메틸-4-이소티아졸릴)-5-이소옥사졸릴)메틸리덴)피페리디닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-에톡시카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-메틸카보닐메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-에톡시카보닐에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-카복시메틸리덴피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 나트륨 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-클로로-1-에톡시카보닐메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-시아노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-옥소에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;

N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노에틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-하이드록시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-메톡시이미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-히드록시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(2-디클로로아세톡시프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(시아노메틸리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염;
N-[(5S)-3-[3-플루오로-4-(4-(1-시아노-3-아미노프로필리덴)피페리디닐)페닐]-2-옥소-5-옥사졸리딘일]메틸티오아세트아미드 및 그의 염산 염;

[제 9 항] 이 화합물은 약제학적으로 허용된 염을 포함한다. 즉 메탄설폰산 염, 푸마렌산 염, 브롬산 염, 시트릭산 염, 말레인산 염, 인산 염, 환산 염, 염산 염, 소듐의 형태 또는 염이 아닌 아민 상태를 포함한다.